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Die Forschung über die Wirkungen und Wirkungsweisen psychotroper Substanzen hat in den letzten Jahren einen unerhörten Aufschwung genommen. Was vordem nur ein erwünschtes Ziel war, ist zu einer neuen Wissenschaft geworden: Psychopharmakologie. Da eine fruchtbare Analyse und Synthese ihrer Probleme nur durch Zusammenarbeit aller Grundfächer (Pharmakologie, Neurochemie, Neurophysiologie, Neurologie, Psychologie und Psychiatrie) möglich wird, ist die Psychopharmakologie eine verbindende, integrierende Forschungsdisziplin. Die ständig anwachsende Literatur dieses komplexen Arbeitsgebietes ist jedoch bisher zwangsläufig über zahlreiche Zeitschriften verstreut, da es bis heute kein Spezialorgan gab, das sich ausschließlich der Psychopharmakologie widmet. Diesem dringenden Bedürfnis zu begegnen, hat sich eine Gruppe von Vertretern der verschiedenen Arbeitsrichtungen der Psychopharmakologie entschlossen, eine neue Zeitschrift „Psychopharmacologia" zu gründen. In ihr sollen die bedeutenden Fortschritte dieses Arbeitsgebietes durch Veröffentlichung experimenteller und klinischer Originalarbeiten, Übersichten der neuesten Literatur sowie kurzer Originalmitteilungen zusammengefaßt werden.

Recent years have witnessed an unprecedented advance in research on the action and effects of psychotropic drugs, and what, formerly, was just a distant goal, has now evolved into a new branch of science: psychopharmacology. As, however, any fruitful analysis and synthesis of its problems can only be attained with the aid of the complete scale of basic sciences (pharmacology, neurochemistry, neurophysiology, neurology, psychology and psychiatry), psychopharmacology constitutes an integrating discipline of research. Owing to the lack of an organ devoted especially to psychopharmacology, the constantly increasing literature pertaining to this complex field of activity has hitherto of necessity been scattered among various periodicals. In order to overcome this drawback, a group of representatives of the various psychopharmacologic sections have engaged in editing a journal, "Psychopharmacologia", in which the publication of original experimental and clinical papers, reviews of recent literature and short original notices will provide a comprehensive survey of the important progress which is being actually achieved in this field of science.

Ces dernières années ont vu un développement sans précédent dans la recherche des effets et du mode d'action des substances psychotropes sur le «Comportement» et ont fait naître une nouvelle science: la Psychopharmacologie. Comme ces problèmes ne peuvent être résolus que par la collaboration des disciplines de base telles que la pharmacologie, la neurochimie, la neurophysiologie, la psychologie et la psychiatrie, la psychopharmacologie est devenue un champ de recherche de première importance. Cependant la littérature toujours croissante en ce domaine de recherche est forcément disséminée dans de nombreux périodiques, puisqu'il n'existe pas encore de journal exclusivement consacré à la psychopharmacologie. Pour répondre à ce pressant besoin un groupe de représentants des diverses disciplines de la psychopharmacologie s'est mis en devoir de rédiger un nouveau journal dans lequel seraient rassemblés les progrès importants de ce domaine, par la publication d'ouvrages originaux expérimentaux et cliniques, ainsi que des rapports sur des questions actuelles.

Richtlinien für die Mitarbeiter siehe am Schluß des Heftes. — Directions to Authors are given at the end of this number. — Directives destinées aux auteurs, voir à la fin du fascicule.

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Psychopharmacologia

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INHALTSÜBERSICHT

Allgemeiner Teil: Die Entwicklung der Persönlichkeit und ihrer Störungen. Psychologische Wegleitung und allgemeine Psychopathologie anhand einzelner psychischer Funktionen. Die Körperbefunde in der Psychiatrie. Einteilung der psychischen Störungen. Verlauf der psychischen Störungen. Die psychiatrische Untersuchung. Ursachen der psychischen Störungen. Vorbeugung und Behandlung · Spezieller Teil: Geistesstörungen in engem Zusammenhang mit Körperkrankheiten. Die „endogenen" Geistesstörungen. Die krankhaften Reaktionen („psychoreaktive" oder „psychogene" Störungen). Persönlichkeitsstörungen in Beziehung zu angeborenen Persönlichkeitsvarianten · Anhang: Das Notwendigste aus der gerichtlichen Psychiatrie: Strafrecht. Bürgerliches Recht. Zivilrecht. Die Gutachtentätigkeit. Forensische Bedeutung der einzelnen Krankheiten. (Von F. MEGGENDORFER †; neu bearbeitet von W. VILLINGER, Marburg/Lahn) · Literatur-Hinweis · Sachverzeichnis · Erklärung der griechischen Ausdrücke.

AUS DEN BESPRECHUNGEN DER NEUNTEN AUFLAGE

„... Es kommt wohl selten vor, daß der Begründer eines wissenschaftlichen Lehrbuches in der Person seines Sohnes einen Nachfolger findet, der sich nicht nur der Tradition verpflichtet fühlt, sondern selber in der vordersten Front der Forschung steht. Diesem Umstand ist es zu verdanken, daß der „Bleuler", der seit bald 40 Jahren in der Schweiz für alle psychiatrischen Fragen am meisten nachgeschlagen und zitiert wird, noch heute eines der besten und modernsten Lehrbücher der Psychiatrie ist."

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1 Harris, H.: J. Amer. Med. Ass. **172**, 11, 1162 (1960)

2 Voelkel, A.: Vortrag Tagg. Dtsch. Sektion Internat. Ges. Psycho-Pharmako-Therapie Nürnberg 30. IV. - 1. V. 1960

3 Tobin, J. M., Bird, I. F., Boyle, D. E.: Dis. Nerv. Syst. **21**, Beiheft 3, 11 (1960).

Psychopharmacologia 1, 357—371 (1960)

Original Investigations · Originalarbeiten · Travaux originaux

Institute for Cardiovascular Research, Praha-Krč, ČSR

The Effect of Long-term Oral Combination of Methylphenidate and Reserpine on the Autonomic Phenomena at Rest and on Inborn and Acquired Reflexes of Dogs*

By

V. Ehrlich, K. Frošková and L. Šlégr

With 4 Figures in the Text

(Received December 18, 1959)

The object of this paper is to contribute towards clarifying the indication of the combined medication of methylphenidate and reserpine, to increase our knowledge of the mechanism of the effect of these two substances, particularly to characterize their antagonism (Cole and Glees 1956) more closely and finally to contribute towards analyzing the mechanisms governing vegetative changes during inborn and acquired reflexes.

Up till now the effect of the combination of reserpine and methylphenidate has been studied experimentally by observation of the behaviour of animals after single injections of large doses only (Cole and Glees, 1956, Davis 1957). With this arrangement the authors found that methylphenidate interferes with the effect of reserpine on the behaviour of monkeys for several hours.

In clinical, especially cardiologic praxis however reserpine is usually applied orally for a long time, methylphenidate is added to it in order to prevent the undesirable "side"- effects without disturbing the desired effect. The object of the present experiments, therefore, is to investigate the action of the combination of the two substances, with an experimental arrangement which corresponds as closely as possible to the way in which these substances are used clinically and which enables the effect of the combination of the two substances on the acquired reactions, i.e. on the adaptation of the organism to its surroundings, to be distinguished from the effect on inborn reactions.

We investigated the effect of long-term oral administration of methylphenidate on dogs, which for two weeks prior to this medication and simultaneously with it received reserpine orally each day. For this purpose we studied the autonomic phenomena at rest, the autonomic reactions during food intake, during the conditioned alimentary reflex and during differential stimulus (Frošková et al. 1957). Both substances

* A preliminary report of these results was made at the "Pharmacological Days" in Plzeň, September 11, 1959.

were given daily in amounts corresponding to the doses used clinically. The effect of the combined medication of reserpine and methylphenidate was compared with the effect of long-term oral medication with reserpine alone (EHRLICH at al. 1958) and that of methylphenidate alone (EHRLICH et al. 1960) studied under the same experimental arrangement.

Methods

Arrangement of experiments. In a sound-proof, constant temperature chamber 228 experiments were carried out with four dogs whose conditioned alimentary reflexes and differential inhibitions to sound signals had previously been worked out. As a rule, the dogs received thirty grams of wet powder, consisting of dried meat and crackers, four times during one experiment. Before the first and last serving, the conditioned signal rang for only two seconds. Before the second and third serving, it rang for ten seconds. After the second feeding, there followed the differential signal, which was never combined with the serving. The period between the beginning of each succesive signal was four minutes. During the experiment we registered the secretion of saliva from an artificial fistula in the parotid gland, the frequency of respiration through a ribbed rubber tube around the thorax, and the pulse and blood pressure changes indirectly from a carotid loop through a special condensor head connected with a capacitance manometer (FROŇKOVÁ, ŠLÉGR 1955a, b). In addition, the blood pressure was taken by auscultation on the carotid loop at the onset of each experiment. The cuff was 2.5 cm broad.

Method of Evaluation. The pulse rate was taken in segments with completed respiratory cycles and expressed in number of beats per minuts. The reflex acceleration of the pulse was the difference between the pulse one minute before the signal, i.e. the pulse at rest, and the pulse during the signal, or at the beginning of food intake. The reflex acceleration of respiration was the difference between the respiration one minute before signal, i.e. respiration at rest, and the respiration during the signal, or at the beginning of food intake. Salivation in the first ten seconds during food intake, or during the signal, was observed in number of drops. The values for conditioned reflexes were taken only from the reflexes preceding the second and third servings in each experiment, when the tone rang in isolation for ten seconds.

For the individual experimental periods, the auscultatory values of blood pressure, respiration and pulse at rest, acceleration of respiration and pulse and, finally, drops of saliva, are given in averages. The statistical significance of the difference between values before medication and values in all other periods of medication was ascertained by the T-test. From the continuous registration of blood pressure the number of cases where the blood pressure rose in reflexes was ascertained. The

number of cases of blood pressure rises is expressed in the percentage of the aggregate number of observations. The statistical significance of difference of incidence blood pressure rise in the individual periods was tested by χ^2.

Medication (Table). With every dog we made one experiment daily. During the first fortnight the dogs received no drugs. In the following weeks the dogs received the drugs, the effect of which was to be investigated, 1 hour before every experiment by oral administration. The total numbers of experiments with those four dogs in every period are:

47 experiments—no drug
medication periods:
1. 49 experiments—0.02 mg/kg reserpine
2. 40 experiments—0.02 mg/kg reserpine + 0.2 mg/kg methylphenidate
3. 31 experiments—0.02 mg/kg reserpine + 0.5 mg/kg methylphenidate
4. 24 experiments—0.02 mg/kg reserpine + 1.0 mg/kg methylphenidate

37 experiments—no drug.

0.02 mg/kg reserpine given daily through all the periods of medication corresponds to 1.4 mg reserpine for a man weighing 70 kg. 0.2 mg/kg methylphenidate given daily in the second period of medication corresponds to 14 mg for a man weighing 70 kg i.e. an average single dose. In the third period of medication the dogs received two and a half time more methylphenidate than in the preceding period. In the next period finally the dogs received the double of the preceding and five times the initial daily dose of methylphenidate. The 37 experiments in the first days after the termination of the combined medication were made in order to ascertain the vanishing of the effect of the drug combination.

Table

No. of experiments:

Dog	Before medication	Reserpine	Reserpine + Methylphenidate			After medication	Total number of experiments
L	10	11	9	9	7	10	56
F	14	14	11	11	10	18	78
B	10	10	10	4	7	9	50
Z	13	14	10	7	—	—	44
Total	47	49	40	31	24	37	228
Dosage in mg/kg body weight by oral way: Reserpine		0.02	0.02	0.02	0.02	—	—
Dosage in mg/kg body weight by oral way: Methylphenidate		—	0.2	0.5	1.0	—	—
Related to man weighing 70 kg: Reserpine		1.40	1.40	1.40	1.40	—	—
Related to man weighing 70 kg: Methylphenidate		—	14.0	35.0	70.0	—	—

Graphic documentation (Fig. 1—4). The mean values of every autonomic phenomenon from all experiments with all dogs in one experimental period is shown in one column. The first column in every line shows values from the period without medication. The next column in the lines shows the mean values from the periods of medication as indicated on the top of the graphs. The last column in every line shows the mean value of the experimental days after finishing the combined medication. Mean values marked by stars differ statistically significantly from the values of the period before medication.

Results

Behaviour and general state of animals. After the third week of receiving reserpine alone the dogs walked into the chamber slowly and no longer jumped into the stand on their own. Their nictitating membrane relaxed, diarrhoea appeared, secretion from the nose increased strikingly, their coats became ruffled and lost their shine. Two dogs, L. and Z., had markedly relaxed nictitating membranes, in the laboratory they trembled violently and their hair fell out in tufts, leaving regions of bare skin covered with scales. After the 31st experiment with reserpine medication, when it was already receiving a larger dose of methylphenidate as well, one of them (dog Z) was found dead in the morning in front of its kennel (Table). The state of the other dogs improved only after medication with both substances had ended.

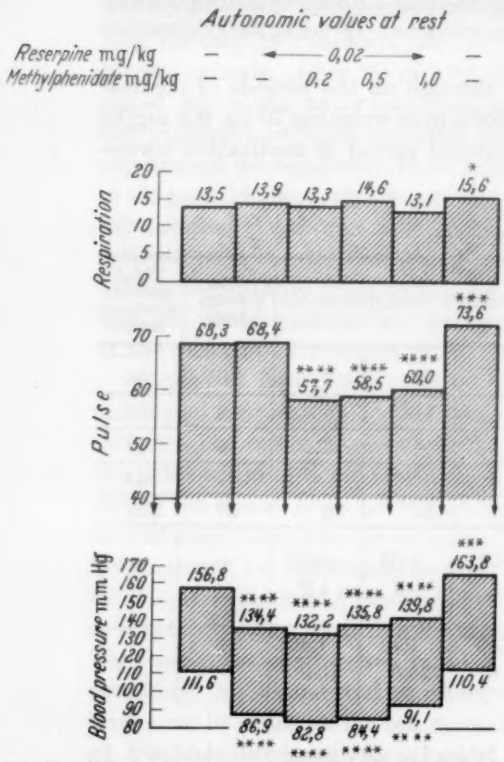
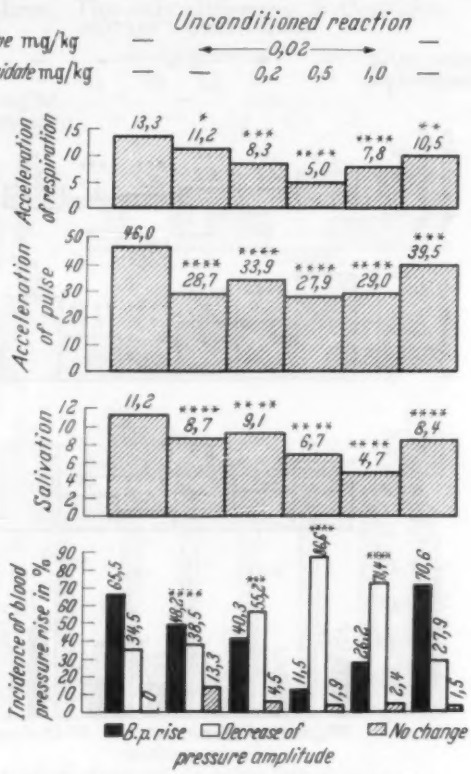


Fig. 1

Autonomic phenomena at rest (Fig. 1). *Respiration at rest* is not significantly changed by medication. In the period after termination of the medication with both substances respiration at rest is significantly more rapid than in the period before medication. *The pulse at rest* is markedly slowed down by combined medication. After termination of the medication the pulse at rest is significantly

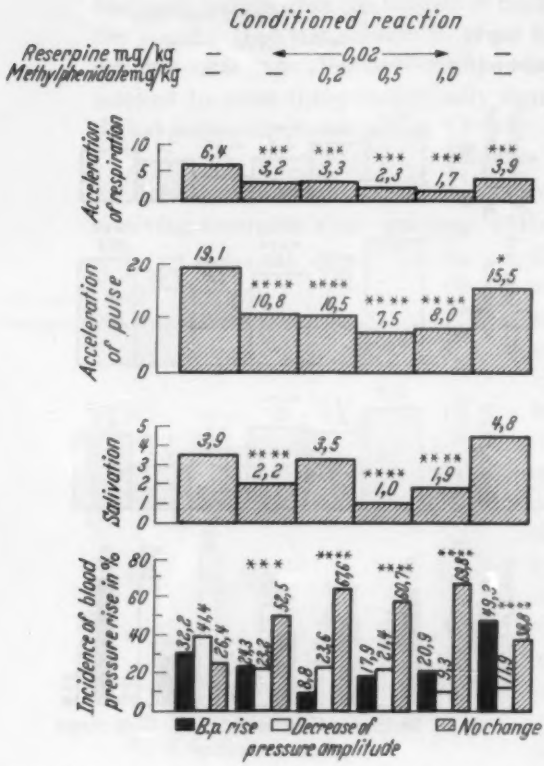
quicker than before medication. *The blood pressure* at rest is significantly lowered by medication, to approximately the same degree in all periods. After termination of the combined medication the diastolic pressure returns to its original value. On the other hand, the systolic pressure is significantly higher than before medication, corresponding to the significantly quicker pulse et rest.

Autonomic reactions during food intake (Fig. 2). The unconditioned *acceleration of respiration and pulse* as well as *salivation* significantly decrease in the period of combined medication. After termination of medication this decrease was less pronounced but was still significant. The incidence of *blood pressure rise* is significantly smaller in all periods of medication. In the majority of cases the diastolic pressure remains unchanged and food intake is accompanied by a decrease in the pressure amplitude. After termination of combined medication the incidence of blood pressure rise during food intake does not differ from that before medication.


Unconditioned reaction
Reserpine mg/kg — — 0,02 —
Methylphenidate mg/kg — — 0,2 0,5 1,0 —
Acceleration of respiration
13,3 11,2 8,3 5,0 7,8 10,5
Acceleration of pulse
46,0 28,7 33,9 27,9 29,0 39,5
Salivation
11,2 8,7 9,1 6,7 4,7 8,4
Incidence of blood pressure rise in %
65,5 34,5 0 49,2 38,5 13,3 40,3 55,2 4,5 11,5 64,1 1,9 26,2 73,8 2,4 70,6 27,9 1,5
B.p. rise
Decrease of pressure amplitude
No change
Statistically significant change against values before medication:
*=P<0,05 **=P<0,02 ***=P<0,01 ****=P<0,001
Fig. 2

Autonomic reactions during conditioned alimentary reflex (Fig. 3). The conditioned *acceleration of respiration and pulse* is significantly decreased in all periods of medication. After termination of medication these changes are less pronounced but remain significant. Conditioned *salivation* is significantly decreased in the period when reserpine is given on its own. In the next period, in which 0.2 mg/kg of methylphenidate is added to the reserpine, the conditioned salivation approaches its original values. In the following periods the conditioned salivation is again significantly decreased. After termination of medication the

conditioned salivation is significantly greater than prior to medication. Conditioned *blood pressure rise* as well as cases when only the pressure amplitude decreases, occur significantly less frequently during medication. In the majority of cases the conditioned stimulus does not produce any change in the blood pressure. After termination of medication the conditioned blood pressure rise is significantly more frequent than before medication.



Statistically significant change against values before medication:
*=P<0,05 ***=P<0,01 ****=P<0,001
Fig. 3

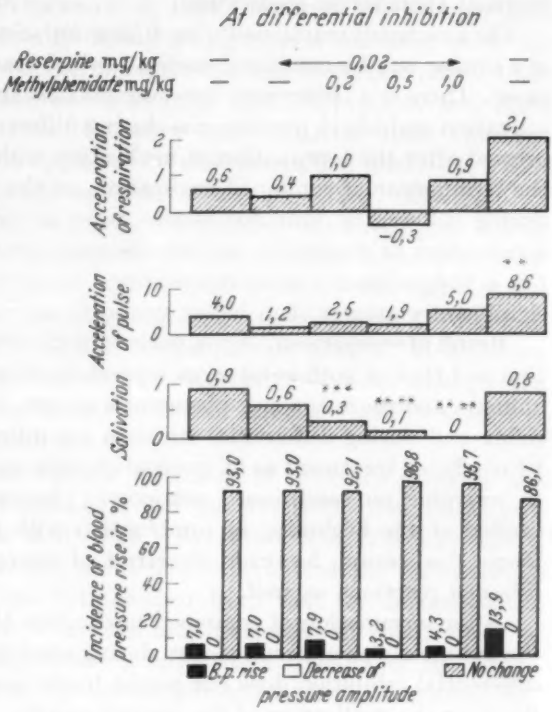
Autonomic reactions during differential stimulus (Fig. 4). *The acceleration of respiration and pulse* during differential stimulus is not significantly influenced by the combination of the two substances. After termination of medication the acceleration of respiration is greater and the acceleration of pulse is significantly greater than before medication. *Salivation* is significantly inhibited by combined medication and finally disappears. After termination of combined medication salivation reaches its original values. The incidence of *blood pressure rise* during differential stimulus is not particularly influenced by medication.

Comparison of results of long-term combined medication with results of long-term medication with reserpine alone and methylphenidate alone.

In earlier work with reserpine alone we gave the same or larger oral doses than in the present experiments, but for a much shorter period. Further the dogs received half doses for practically the same period as in the present experiments. Symptoms of intoxication were not observed. The dogs, however, became more wary and moved less (EHRLICH et al. 1958). When 0.02 mg/kg reserpine is given for a longer period in the present experiments, symptoms of intoxication appear in addition to the slowing down and lessening of movement. This state remains in the period of combined medication, in which one dog even dies (Table 1).

The behaviour and general state of the animals during combined medication thus corresponds to the effect of reserpine alone, depending on the duration of the medication and on the daily amount of reserpine.

Combined medication acts on the *autonomic phenomena* at *rest* (Fig. 1) in a similar way as reserpine alone. The only difference is that after termination of medication with reserpine alone the respiration and blood pressure at rest did not differ significantly from the values prior to medication and the pulse at rest was significantly slower (EHRLICH et al. 1958); after termination of combined medication, however, the respiration and pulse at rest is significantly more rapid and the systolic blood pressure is significantly higher than in the period prior to medication.



Statistically significant change values before medication:
**=P< 0,02 ***=P< 0,01 ****=P< 0,001

Fig. 4

The autonomic phenomena of *the unconditioned alimentary reflex* (Fig. 2) are affected by combined medication in a similar way as by medication with reserpine alone. The autonomic phenomena of the *conditioned alimentary reflex* (Fig. 3) is also affected by combined medication in the same way as by reserpine alone, given for almost the same period. There are, however, two striking differences: firstly, methylphenidate in dosages of 0.2 mg/kg annuls the decrease in conditioned salivation. In further periods, when on the one hand the effect of continuous reserpination accumulates and on the other hand methylphenidate is given in two and a half times and then five times greater daily doses, the conditioned salivation again decreases. Secondly, after completing long-term medication with reserpine alone, the conditioned acceleration of the pulse was smaller than during medication, the diminution of conditioned salivation

and the suppression of the conditioned blood pressure rise were the same as during medication. After termination of the combined medication, on the contrary, the decrease in acceleration of pulse and respiration is less pronounced than during medication; the conditioned salivation is no longer decreased and the conditioned blood pressure rise is much more frequent than before medication.

The autonomic reactions during *differential stimulus* (Fig. 4) are affected in a similar way by combined medication as by medication with reserpine alone. There is a difference, however, in that the acceleration of pulse, salivation and blood pressure rise during differential stimulus were suppressed after the termination of medication with reserpine alone. After the termination of combined medication, on the contrary, the salivation during differential stimulus is the same as prior to medication, the acceleration or respiration is insignificantly greater, the blood pressure rise is insignificantly more frequent and the acceleration of the pulse is significantly greater than before medication.

Result of comparison. A comparison of the effect of combined medication and that of both substances separately shows that the behaviour of animals, and the autonomic phenomena at rest, during the unconditioned reflex and during differential stimulus are influenced in the same way by combined treatment as by medication with reserpine alone. The effect of reserpine on conditioned autonomic phenomena can be somewhat limited at the beginning of combination with methylphenidate. With longer medication, however, the effect of reserpine prevails on the conditioned reactions as well.

After termination of combined medication the effect of reserpine on the autonomic phenomena at rest, during conditioned reflexes and during differential inhibition does not persist to the same degree as it did after finishing the medication of the reserpine alone. After combined medication has been terminated the autonomic reactions during conditioned reflexes are less inhibited than after medication with reserpine alone and the autonomic phenomena at rest and during differential stimuli are not inhibited at all, or even exceed the values prior to medication.

The effect of oral methylphenidate alone, found earlier in the same experimental set up (EHRLICH et al. 1960) — significant improvement of differentiation with simultaneous increase of conditioned reactions — does not appear in any period of combinated medication nor after its termination.

Discussion

The manifestation of intoxication with reserpine. The symptoms of intoxication, which were observed with doses of 0.02 mg of reserpine daily, correspond to the symptoms universally described (BEIN 1953, BEIN et al. 1953, CRONHEIM and TOEKES 1955, PLUMMER et al. 1954). It was shown, that dogs survive a dose of 0.035 mg/kg of reserpine longer

than 6 months (PLUMMER et al. 1954). In our experiments, however, after the 31st dose of 0.02 mg/kg reserpine, one dog was found dead the next morning in front of its kennel. During this night, late in November, the temperature fell to 2° C. A post-mortem examination showed no macroscopic changes. We suppose that due to decreased mobility (BEIN 1953, BEIN et al. 1953, PLUMMER et al. 1954, CRONHEIM and TOEKES 1955) the dog did not crawl into its kennel at night as it was used to do but fell asleep outside. As its thermoregulation was disturbed (BEIN 1953, BEIN et al. 1953, TADDEI and RAMOINO 1953, SCHNEIDER and EARL 1954, PLUMMER et al. 1954, EVERETT et al. 1955) it died. Thus the symptoms of intoxication appeared — and one animal died — at a time when the dogs were already receiving methylphenidate. Methylphenidate neither prevents nor removes intoxication with reserpine during long-term medication with reserpine. In earlier experiments with reserpine alone intoxication was not produced, therefore the time of disappearance of intoxication symptoms after termination of combined medication can not be compared and it is not possible to ascertain whether methylphenidate accelerates this process, even though the symptoms of intoxication disappeared with striking rapidity after termination of combined medication.

The effect of reserpine. Single injections of reserpine decrease the conditioned reactions (WEISKRANTZ and WILSON 1955, 1956, GLIEDMAN and GANTT 1956, SMITH et al. 1956, 1957, COOK and WEIDLEY 1957). With an experimental arrangement which permitted the influence on conditioned reflexes to be distinguished from that on unconditioned reflexes, we showed that long-term administration of small doses of reserpine has a specifically different impairing influence on the conditioned reactions to that on the unconditioned reactions. Reactions during differential inhibition did not decrease significantly except for salivation (EHRLICH et al. 1958).

Reserpine diminishes the contents of catecholamines in all tissues where these substances are usually found (BEJRABLAYA et al. 1958, BURN and RAND 1958, CARLSSON et al. 1958, KRAYER and FUENTES 1958, MIRKIN 1958, MOLINATTI et al. 1958, MUSCHOLL and VOGT 1957, 1958, PAASONEN and KRAYER 1958, WAUD et al. 1958, KRONEBERG and SCHÜMANN 1959), also in the mesodiencephalic region (VOGT 1954, HOLZBAUER and VOGT 1956, TSIEN et al. 1956). Small repeated doses of reserpine are equally as effective as large single doses (MUSCHOLL and VOGT 1958, WAUD et al. 1958). The simultaneous removal of serotonin from the same regions (PLUMMER et al. 1954, SHORE et al. 1955, BRODIE et al. 1955, PAASONEN and VOGT 1956, PLETSCHER et al. 1956) suppresses the adrenergic mechanisms (GORDON et al. 1956). Long-term administration of reserpine thus decreases the adaptibility of the organism to external influences by diminishing the contents of catecholamines and serotonin

of the mesodiencephalic part of the reticular formation. It can be inferred from our results that the adrenergic mesodiencephalic mechanism, which participates in the arousal of the cerebral cortex (PORTER 1952, 1957, DELL et al. 1954, SIGG et al. 1955, ANOCHIN 1956, ROTHBALLER 1956, 1957, DELL 1957, JASPER 1957, OLDS 1959) also plays an important part in acquired reflexes and their differentiation. This conclusion is in agreement with the recently ascertained fact that the reticular formation is connected with the mechanism of acquired reflexes and differentiations (GRASTYAN et al. 1956, SHARPLESS and JASPER 1956, GASTAUT 1957, IGRAM 1957, JASPER 1957, DOTY 1959, GALAMBOS 1959).

The effect of methylphenidate. Methylphenidate, although not an amine, has a very similar effect on CNS as amphetamine (MEIER et al. 1954, COLE and GLEES 1956, DAVIS 1957), a sympathomimetic amine, not derived from catecholamines. It was shown that 0.19 mg of methylphenidate administered over a long period, improved differential inhibition of all reactions while simultaneously increasing the conditioned reflexes (EHRLICH et al. 1960). Methylphenidate added to reserpine in these experiments changes only the conditioned salivation of all the conditioned reactions and then only in the first period (Fig. 3). Otherwise, however, not even multiple doses of methylphenidate fundamentally change the effect of reserpine either on the behaviour and state of the animals or on the autonomic phenomena at rest (Fig. 1), on unconditioned (Fig. 2) and conditioned reactions (Fig. 3) and on reactions during differentiation (Fig. 4). This shows that long-term administration of methylphenidate cannot affect the CNS and other tissues of which the catecholamine content has been substantially lowered for a long time, in a similar way as sympathomimetic amines, not derived from catecholamines, do not in acute experiment affect the peripheral blood circulation, the nictitating membrane and the spleen with substantially lowered catecholamine content (BURN and RAND 1958). It can thus be inferred that the effect of methylphenidate on CNS is sympathomimetic and mediated by catecholamines.

Single injections of methylphenidate cancelled the effect of previous injections of reserpine on the behaviour of monkeys (COLE and GLEES 1956, DAVIS 1957), presumably because some hours after first injections of reserpine the tissue contains still enough catecholamines to be activated by methylphenidate. When, however, methylphenidate is added to the long-term administration of reserpine, the successively release of catecholamines seems to be so effective that there is not enough of the catecholamines left for the methylphenidate to act.

Although reserpine is rapidly destroyed and excreted from the organism (NUMEROF et al. 1955), its effect after long-term administration disappears only very gradually, particularly its effect on the pulse at

rest and on the acquired reflexes (EHRLICH et al. 1958). Some effects obviously last until the catecholamines and serotonin in the tissues attain their usual concentration. If, after simultaneously terminating the administration of both substances, the effect of the reserpine disappears rapidly (Figs. 3, 4) and the autonomic phenomena even overshoot (Figs. 1, 3, 4), it must be inferred that the slowly increasing amount of catecholamines already enables the methylphenidate to have a certain sympathomimetic effect even though improved differentiation is not yet seen.

From our results it can thus be inferred that the antagonism of the effect (COLE and GLEES 1956) of both substances consists in the reserpine diminishing the content of catecholamines of the tissues, while the methylphenidate acts through the catecholamines. Our results confirm the clinical experience that methylphenidate strongly antagonizes the effect of reserpine if administration of the latter has ended. During long-term simultaneous administration of both substances the combination of reserpine and methylphenidate cannot be expected to have a different effect to that of reserpine alone, at least with non-psychiatric diseases.

Summary

The influence of long-term oral medication of 0.02 mg/kg reserpine daily in combination with 0.2, 0.5 and 1.0 mg/kg of methylphenidate on autonomic phenomena at rest, on the unconditioned and conditioned alimentary reflex and its differentiation were investigated in 4 dogs in 228 experiments.

Intoxication symptoms appeared in the third week of daily administering 0.02 mg of reserpine. Combination with methylphenidate did not prevent or remove intoxication. After a month of reserpination one dog died.

Long-term combination of oral medication changes *the autonomic phenomena at rest and during the reflexes* in the same way as medication with reserpine alone. Methylphenidate merely balances the effect of reserpine on the conditioned salivation and this only in the first period of combined medication. After combined medication has ended, the influence of the reserpine does not last, as it does after medication with reserpine alone, but the autonomic phenomena at rest, during acquired reactions and their differentiations return to normal and sometimes even overshoot. The characteristic effect of medication of methylphenidate alone — improved differentiation with simultaneous increase of conditioned reflexes — does not occur either during combined medication nor after its termination.

The results of our investigations indicate that:

1. Long-term administration of reserpine decreases the adaptibility of the organism to its surroundings, apparently because the adrenergic mechanism of the mesodiencephalic part of the reticular formation, which plays an important role in the electrophysiological mechanism of arousal, also participates substantially in the acquired reflexes and their differentiations.

2. Methylphenidate on its own causes better adaptation of the organism to its surroundings apparently by acting through the catecholamines on the adrenergic mechanism of the mesodiencephalic region. In the case of long-term combination with reserpine methylphenidate cannot be effective because the content of catecholamines of the tissue of the reticular formation is substantially diminished.

3. The slowly increasing concentration of catecholamines after simultaneous ending the medication of both substances apparently enables the remnants of methylphenidate to have a sympathomimetic effect.

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Blocking of the Cortically Induced Behavioral Attention (Orienting) Response by Chlorpromazine*

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With 3 Figures in the Text

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Introduction

There is an impressive consensus that psychotropic drugs like chlorpromazine and its congeners have an important site of action on the brain stem reticular formation. This concept is derived mainly from the following electroencephalographic and behavioral studies.

Electroencephalographic studies. First, chlorpromazine causes in the EEG a pattern of slow activity (synchronization). Although this evidence is not conclusive, the increased synchronization has by most authors been attributed to a depressant influence of chlorpromazine on the reticular formation. Such slowing of the EEG, persisting for several hours, has been recorded in a great number of studies in animals and man following injection of 1 to 20 mg/kg, the threshold dose varying with the route of administration and the species of animals (for references, see LEHMANN 1956; BOVET et al. 1957; UNNA and MARTIN 1957; KILLAM and KILLAM 1958). However, the doses required to modify the spontaneous cerebral electrical activity are generally higher than the usual therapeutic doses and those affecting the behavior of animals. In unrestrained conscious cats consistent changes in the EEG were observed with doses of 3 to 4 mg/kg intravenous injection and 15 to 20 mg/kg intraperitoneally (BRADLEY and HANCE 1957).

Second, chlorpromazine reduces the EEG arousal (desynchronization) produced by direct reticular and peripheral sensory stimulation (HIEBEL et al. 1954; LONGO et al. 1954; RINALDI and HIMWICH 1955; BRADLEY and co-workers 1957, 1958, 1959; UNNA and MARTIN 1957; BOVET et al. 1957; MONNIER 1957; KILLAM and KILLAM 1957). As pointed out by BRADLEY and co-workers the effect of chlorpromazine on the EEG arousal elicited by direct reticular stimulation is relatively small when compared with the effect produced by peripheral sensory stimulation.

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Thus, the EEG arousal to peripheral stimulation was completely blocked by chlorpromazine with doses between 2 and 4 mg/kg intravenously. On the other hand, the threshold for EEG arousal on direct reticular stimulation was only slightly elevated by chlorpromazine even when large doses (up to 9 mg/kg) were used, an observation which is in agreement with the report by KILLAM and KILLAM (1957, 1958). (Some contradictary reports will be discussed later.) Comparable values (2 to 5 mg/kg) for the blocking of the peripherally induced EEG arousal have been given by UNNA and MARTIN (1957) and BOVET et al. (1957). Based on a study of single unit activity in the reticular formation, BRADLEY (1957) suggested that chlorpromazine exerts a more specific depressant action on the sensory collateral inflow to reticular neurons rather than acting on the reticular neurons themselves. This idea was further elaborated in subsequent combined EEG and behavior studies (BRADLEY and KEY 1958; BRADLEY 1959). This view is also corroborated by the observations that chlorpromazine prolongs the recovery cycle of reticular neurons to peripheral stimulation but only slightly elevates the threshold for EEG arousal from direct reticular stimulation (KILLAM 1957; KILLAM and KILLAM 1957, 1958; UNNA and MARTIN 1957). On the other hand, comparatively small doses of barbiturates abolish the EEG arousal to reticular stimulation (KING 1956; KILLAM and KILLAM 1956, 1958; BRADLEY and KEY 1958) and block conduction of impulses within the reticular formation (FRENCH et al. 1953), chlorpromazine does not (KILLAM and KILLAM 1957, 1958; BRADLEY and HANCE, cit. BRADLEY 1957, 1959).

Behavioral studies. Chlorpromazine in doses of 1 to 5 mg/kg reduces the spontaneous locomotor activity of mice (COURVOISIER 1956a, b), rats (BOYD and MILLER 1954; ALEMA and SERGIO 1957; GATTI 1957), cats (BRADLEY and HANCE 1957), and monkeys (DAS et al. 1954; BARUK et al. 1957). To obtain a similar effect with phenobarbital in mice subanesthetic doses must be employed (COURVOISIER 1956a). Chlorpromazine-treated animals furthermore become more indifferent to the environment and to various external sensory stimuli (auditory, tactile and visual) which normally would arouse the animal, whereas considerably higher doses are necessary to elevate the threshold for behavioral arousal from stimulation of the reticular formation (KILLAM 1957; BRADLEY and KEY 1958). These effects on behavior parallel those on EEG arousal to peripheral and reticular stimulation. BRADLEY (1957) observed that cats that failed to respond to tactile stimuli were still responsive to painful stimuli. Finally, chlorpromazine-treated animals become more indifferent in their search for food or water (ARCHER 1954; GUHA et al. 1954; NAESS and RASMUSSEN 1958).

However, no studies have dealt with the effects of chlorpromazine or other psychotropic drugs on the "arousal" or "attention" response

which can be elicited by electrical stimulation of the cerebral cortex and amygdaloid nuclear complex. Stimulation of certain cortical areas has been shown to produce in the EEG a pattern of desynchronization, an effect which has been assumed to be mediated through projections to the brain stem reticular formation or the intralaminar and midline thalamic nuclei (for review and references, see KAADA and JOHANNESSEN 1960). According to these authors, the responsive cortical areas in the cat include (i) the cortex of the medial frontal surface, the cingulate and hippocampal gyri, (ii) the intermediate lateral frontal cortex, (iii) a large temporo-occipital field, (iv) the orbito-insulo-temporal polar region, and (v) a weaker parietal field. In the unanesthetized animals stimulation of the same cortical areas elicits a characteristic behavioral attention response which consists of arrest of ongoing spontaneous activities, increased alertness, followed by searching movements, usually toward the contralateral side (for review and references, see FANGEL and KAADA 1960).

As emphasized by the latter authors this attention or searching response is probably identical with the orienting or investigatory reflex elicited by PAVLOV in 1910 (see PAVLOV 1928, vol. 1, p. 134). According to GLIEDMAN and GANTT (1956), this externally induced orienting reflex is eliminated in dogs by 2.5 mg/kg of chlorpromazine. Similar behavioral and EEG responses may be induced from part of the amygdaloid nuclear complex (cf. URSIN and KAADA 1960a) and from the intralaminar, dorsomedial and anterior thalamic nuclei (AKERT 1952). With higher stimulus intensities this attention response, when induced from certain points in the cingulate and temporal cortex and in the amygdala, may develop into a fear-like reaction, terminating in flight. Similarly, the externally evoked orienting reflex may be associated with marked fear when the stimulus is sufficiently strong (ROBINSON and GANTT 1947, p. 233).

It was suggested by one of us (KAADA 1959) that a possible therapeutic site of action of chlorpromazine might be, not only on the input-side of the reticular formation receiving impulses from the peripheral sensory organs, but also on these telencephalic "attention areas" or on the neurons of the midbrain reticular formation or intralaminar and midline thalamic nuclei which receive afferents from the cerebral cortex and amygdala. Descending impulses from some of these cortical fields are known to some extent to converge on the same brain stem reticular neurons as receive sensory information (BAUMGARTEN et al. 1954; SCHEIBEL et al. 1955; HERNÁNDEZ-PEÓN and HAGBARTH 1955; FRENCH et al. 1955).

In the present study the effect of chlorpromazine on the behavioral attention response induced in cats from the cerebral cortex, amygdala and intralaminar thalamic nuclei has been studied and the results have

been compared with the effect on the arousal responses elicited from mesencephalic reticular and posterior hypothalamic areas. Electrodes were implanted into all the regions mentioned, and the stimulus threshold determined before and after the injection of varying doses of chlorpromazine.

Material and Methods

Twenty adult cats were used. In each animal usually 4 bipolar needle electrodes, insulated except for the tips and with an interpolar distance of less than 0.5 mm, were implanted through small burr holes under pentobarbital (Nembutal) anesthesia in the following structures: the mesencephalic reticular formation, the amygdala, the midline or intralaminar thalamic nuclei (or the posterior hypothalamus), and the cerebral cortex (the anterior cingulate or temporal areas). The temporal electrodes were situated in the lower portion of the posterior ecto- and suprasylvian gyri. The animals were allowed three or four days to recuperate, and the freely moving cats were then stimulated through the implanted electrodes using square wave pulses of 8 msec' duration and a frequency of 40 c.p.s. for about 5 seconds. The stimulus intensity was gradually increased and the threshold of the behavioral attention or flight responses was determined from each site of stimulation. This procedure was repeated once 15 or 30 minutes later. Chlorpromazine (Largactil), prepared freshly for each experiment, was then administered intraperitoneally, usually beginning with a dose of 1 or 2 mg/kg, or less. The thresholds were then checked every half or one hour (occasionally every $^1/_4$ hour) over a 4-hours period. During this period sometimes a second and a third dose of the drug was injected at intervals and amounts indicated in Figs. 2 and 3. The animals were then allowed to recover and in most cases a final determination of the threshold was carried out the next day, 18 to 24 hours later.

Care was taken not to stimulate each point more than a very few times above threshold values in order to avoid habituation of the arousal reaction which is known to follow natural sensory stimulation (Sharpless and Jasper 1956; Key and Bradley 1958). Control experiments without chlorpromazine showed that the threshold remained fairly constant over a 4- to 6-hours period when the same procedure was employed as in the animals which received the drug.

At the termination of the experiments all electrode placements were identified histologically.

Results

1. The attention response. The criteria used for deciding when behavioral attention had occurred on stimulation were arrest of spontaneous activities, such as walking or licking, with signs of arousal or alertness (attentive facial expression with opening if the eyes, retracting of

the nictitating membrane, pupillary dilatation, raising of the head). On stronger cortical, amygdaloid, and intralaminar thalamic stimulation, these signs of arousal or awakening of the animal were followed by movements of an orienting character consisting of quick and anxious glancing or searching movements, usually towards the contralateral side. Similarly, on mesencephalic reticular and hypothalamic stimulation the threshold criteria used were arrest of spontaneous occupation and the signs of arousal just mentioned. However, from these locations the subsequent searching movements, whether associated with fear (flight) and anger or not, were usually directed towards both sides without the contralateral orienting movements which in most cases were characteritic of the cortical, amygdaloid, and thalamic "attention areas".

It was found that the arousal responses elicited by hypothalamic and midbrain reticular stimulation and which, on stronger stimulation, developed into flight or anger, were less influenced by chlorpromazine than was the arousal associated with contralateral orienting movements (the attention response). The former cases will be described separately below under the heading "the fear response".

The cerebral cortex. Chlorpromazine in doses of 0.5 to 1 mg/kg, given intraperitoneally, constantly produced an increase in threshold or a complete blocking of the behavioral attention response induced from the temporal and anterior cingulate cortex. Representative examples are given in the graphs in Fig. 1a and b, Fig. 2a—c and Fig. 3a and b. A dose of 0.3 mg/kg of the drug caused no significant change in the threshold, whereas with a dose of 0.5 mg/kg there was a definite increase but no complete blocking of the effect (Fig. 1a). At a dose of 1 to 2 mg/kg the response was frequently not elicitable even with the highest stimulus intensities employed (30 volts). This depressant effect of chlorpromazine was apparent at the first stimulation 15 minutes after the administration of the drug and was ordinarily maximal within 30 minutes. In some animals the threshold again decreased 4 to 6 hours after the injection (Fig. 1b; Fig. 2a; and Fig. 3b). However, usually the influence was of longer duration. Threshold determinations on the following day (18 to 24 hours after the injection) showed return to approximately the original values (Fig. 1a; Fig. 2b and c; Fig. 3b).

Under the influence of the drug (1 to 2 mg/kg) the cats became less active and more indifferent towards external simuli. At 1 mg/kg, or more, the behavioral attention response to a low-pitched tone of 2 seconds' duration from a loudspeaker placed at a fixed distance from the head was abolished concomitantly with the cortically induced attention response (Fig. 1b).

The reticular formation. When comparing the influence of chlorpromazine on the attention response induced from the cerebral cortex

with the arousal elicited by stimulation of the mesencephalic reticular formation there was a striking difference. During the blocking of the former the threshold for the reticular response remained essentially unaltered with doses up to 10 mg/kg (Fig. 1a and b; Fig. 2a and b) or showed only a small rise (Fig. 2d). The bared tip of the electrodes were in all animals yielding behavioral arousal situated within the reticular formation just ventrolateral to the periaquaeductal gray, 2 to 3 mm from the midline, at the level of the superior colliculi.

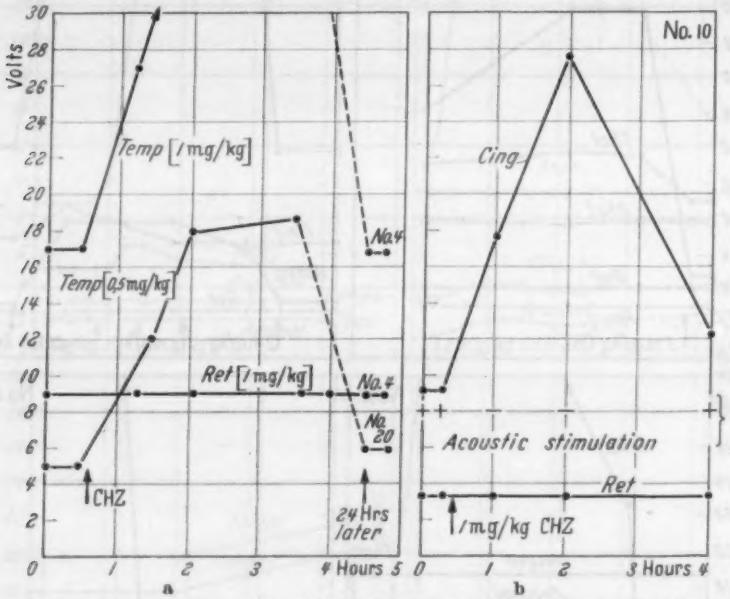

Fig. 1a and b. Effect of 0.5 and 1 mg/kg of chlorpromazine, given intraperitoneally, on the stimulus threshold for the behavioral attention response induced from (a) the temporal (*Temp*) and (b) the anterior cingulate (*Cing*) cortex, as well as for the arousal evoked from the reticular substance of the midbrain (*Ret*). (+): behavioral attention to acoustic stimuli, (—): no such effect. Note rise of the threshold of the cortically induced response and no effect on the response elicited from the reticular substance

Amygdala and thalamus. In general, the attention responses induced from the basolateral division of the amygdala and the intralaminar thalamic nuclei appeared, with regard to susceptibility to chlorpromazine, to take an intermediate position between those reactions elicited from the cerebral cortex and those evoked from the midbrain reticular formation (Fig. 2a and b). Thus, there was at most thalamic (Fig. 2a) and amygdaloid sites (Fig. 2b) a moderate but significant rise in threshold at doses of 2 mg/kg of chlorpromazine. However, the threshold from other points within these structures was less influenced by this dose (Fig. 2a, amyg.), whereas from other sites there was a considerable increase in threshold (Fig. 2d).

2. The fear response. Three of the electrodes in the mesencephalic reticular substance and three electrodes in the dorsal part of the posterior

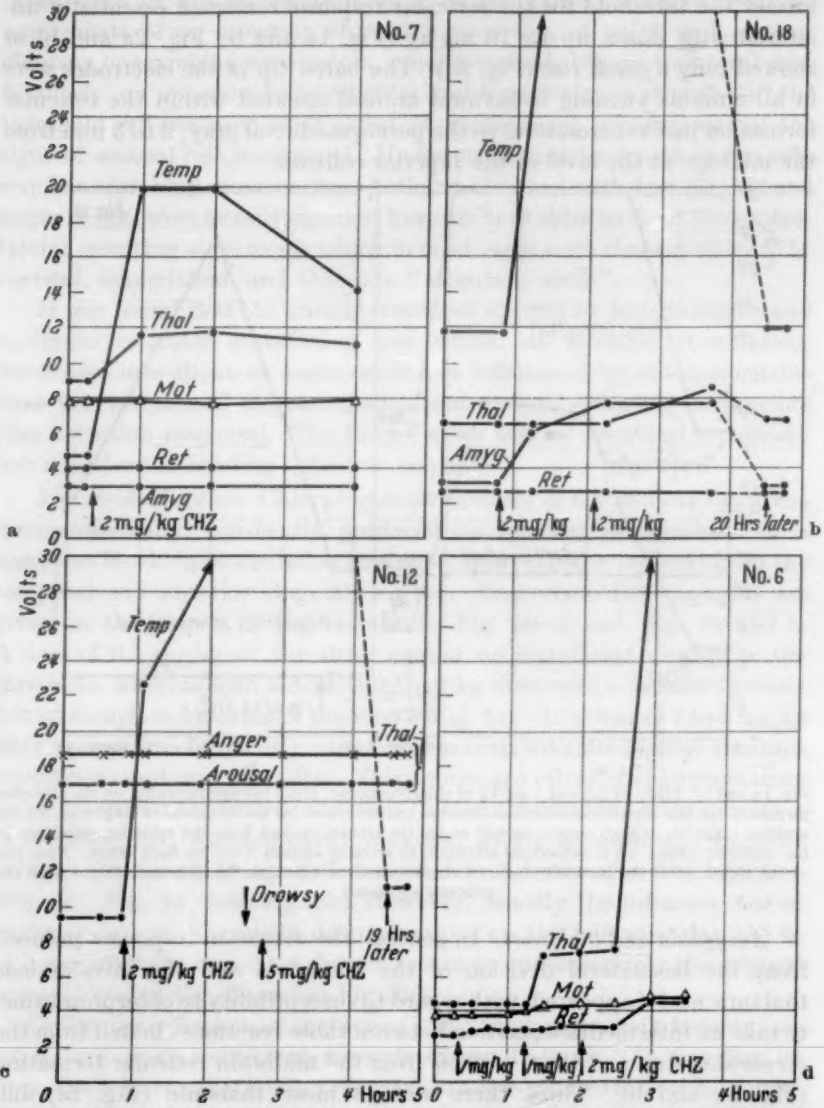

Fig. 2a—d. Effects of 1—2 mg/kg of chlorpromazine, or more, on the stimulus threshold for the behavioral attention response induced by temporal cortical (*Temp*), intralaminar thalamic (*Thal*) and amygdaloid (*Amyg*) stimulation, and for the arousal to mesencephalic reticular (*Ret*) excitation. a—d from four different experiments. Effects on stimulus threshold of cortically induced movements (*Mot.* in a and d) and of anger response produced by thalamic stimulation (c)

hypothalamus were situated at points from which a typical fear (flight) response was evoked, preceded by behavioral arousal (Fig. 3). The

threshold for the arousal as well as for the flight elicited from all these electrode sites remained on the whole unchanged with doses up to 7 or

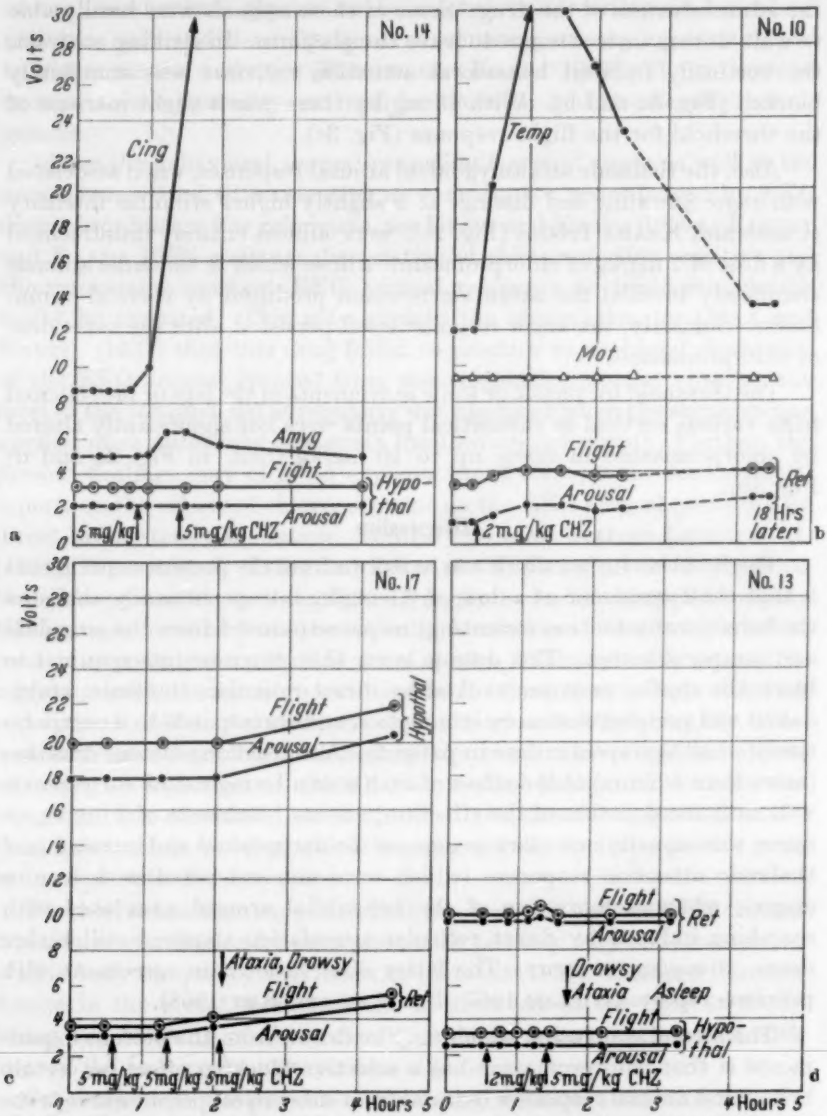

Fig. 3a—d. Effects of chlorpromazine, in doses indicated, on the stimulus threshold for the behavioral attention response elicited by stimulation of the anterior cingulate (*Cing*) and temporal cortex (*Temp*) and amygdala (*Amyg*), and for the arousal and fear (*Flight*) produced from the posterior hypothalamus (*Hypothal*) and mesencephalic reticular substance (*Ret*). Effects on stimulus threshold of cortically induced movements (*Mot*). a—d from four different experiments

10 mg/kg of chlorpromazine. Under the influence of such relatively high doses the animals, when left undisturbed, usually became drowsy, ataxic,

or appeared asleep. In spite of such obvious signs of heavy intoxication threshold stimulation produced the arousal and flight responses as before the administration of the drug. Some of these animals were hardly able to walk during their attempt to leave the platform. In striking contrast, the cortically induced behavioral attention response was completely blocked (Fig. 3a and b). With 15 mg/kg there was a slight increase of the threshold for the flight response (Fig. 3c).

Also, the thalamic and amygdaloid arousal responses, when associated with *anger* (growling and hissing) at a slightly higher stimulus intensity (URSIN and KAADA 1960a) (Fig. 2c), were almost entirely uninfluenced by a dose of 7 mg/kg of chlorpromazine, a dose which in the same animals completely blocked the attention reaction produced by cortical stimulation. Similarly, the anger response itself persisted after the same dose of chlorpromazine.

The threshold for phasic or tonic movements of the legs or face elicited from various cortical or subcortical points were not significantly altered by chlorpromazine in doses up to 10 mg/kg (mot. in Fig. 2a and d; Fig. 3b).

Discussion

The first conclusion which can be drawn from the present experiments is that chlorpromazine at a dose of 0.5 mg/kg intraperitoneally abolishes the behavioral attention (orienting) response induced from the cingulate and temporal cortex. This dose is lower than the amounts required to block the similar response evoked by direct reticular, thalamic, amygdaloid and peripheral sensory stimulation and corresponds to a comparatively small therapeutic dose in patients. Also, the long-lasting duration (more than 4 hours) of the effect of such a small, single dose corresponds well with the duration of the effect in patients. Amounts of 2 mg/kg, or more, were usually necessary to depress the amygdaloid and intralaminar thalamic attention responses (which were not associated with fear or anger); whereas depression of the behavioral arousal associated with searching induced by direct reticular stimulation required still higher doses, 10 mg/kg, or more. The latter observation is in agreement with previous reports (KILLAM 1957; BRADLEY and KEY 1958).

The second conclusion which may be drawn from the present experiments is that chlorpromazine has a selective blocking effect on certain behavioral arousal responses induced from subcortical points whereas the arousal induced from other sites are quite resistant to the drug. It seems clear that the behavioral alerting associated with fear (flight) or anger is less influenced as compared with the alerting combined with searching (orienting) movements only, without obvious signs of emotional expressions. Even amounts of 10 to 15 mg/kg of chlorpromazine, which

caused overt signs of intoxication (drowsiness and ataxia), had no or only a slight effect on the arousal induced through these same electrodes. The arousal mechanism appears to be related to a variety of functional activities such as different patterns of emotions, sensory experience, and to higher mental activities (FANGEL and KAADA 1960). The subcortical arousal areas apparently are not functionally and structurally homogenous.

Since the behavioral arousal preceding fear and anger as well as the arousal associated with orienting movements are accompanied by EEG desynchronization (for references, see URSIN and KAADA 1960a; FANGEL and KAADA 1960) a similar dissociation of chlorpromazine-sensitive and chlorpromazine-resistant EEG arousal responses to brain stimulation might be expected. This may explain the observation by UNNA and MARTIN (1957) that this drug failed to produce as profound depression of the EEG arousal induced from mesencephalic reticular sites (at the level of the red nucleus) as regularly was observed when the stimulus was applied more anteriorly (the exact localization not given). Further, the present findings may offer an explanation of some of the controversial reports on the effects of chlorpromazine on the EEG arousal produced by direct brain stem stimulation. Contrary to most authors LONGO et al. (1954), HIEBEL et al. (1954) and RINALDI and HIMWICH (1955) reported that chlorpromazine in doses of 2 to 3 mg/kg had a blocking effect on the EEG arousal evoked from the reticular formation. This divergence has been interpreted as being due to a species difference, the arousal in rabbits possibly being more sensitive to the drug than in cats (KILLAM and KILLAM 1958). An alternate explanation is that functionally different structures have been studied by the various investigators. Thus, according to LONGO et al. (1954), "the rostral portion of the reticular formation was stimulated at the level of the anterior hypothalamus". This, however, is an area which is not generally included in the term brain stem reticular formation.

Further, it has been suggested that the depression of the EEG arousal to reticular stimulation by chlorpromazine possibly may be secondary to a fall in body temperature (KILLAM and KILLAM 1957). However, no such change in the rectal temperature was observed in the present study during the blocking of the cortically induced behavioral arousal with doses of 0.5 to 2 mg/kg intraperitoneally

Consistent with the present observations, KILLAM (1957) and KILLAM and KILLAM (1958) found that chlorpromazine elevated the threshold at which the "behavioral awakening response" from "the diffuse thalamic projection system" could be elicited whereas the same dose had only slight effect on the behavioral arousal from stimulation of the reticular formation.

Pertinent to the problem under discussion are also the reports by OLDS et al. (1957, 1958, 1959) who observed that chlorpromazine at doses of 2 mg/kg injected intraperitoneally caused a depression of the rate of self-stimulation through electrodes implanted in the anterior septal, ventral posterior hypothalamic, amygdaloid, hippocampal and cingulate cortical regions. On the other hand, the drug had no or only little effect on the avoidance or escape reaction characteristic of self-stimulation of the greater part of the reticular formation and the dorsal posterior hypothalamus (OLDS 1959). From other studies it is known that stimulation of all of the areas mentioned may produce EEG desynchronization (hypothalamus: MURPHY and GELLHORN 1945; brain stem reticular formation: MORUZZI and MAGOUN 1949; amygdala and cerebral cortex: KAADA 1951, 1960; KAADA and JOHANNESSEN 1960). Therefore the findings of OLDS and co-workers, like ours, may be taken to indicate the chlorpromazine has a selective blocking effect on certain types of arousal responses, the one associated with escape reactions being relatively resistant.

According to KILLAM and KILLAM (1956, 1957) chlorpromazine at doses of 2—8 mg/kg also blocks the 3—6 /sec. rhythmic activity which can be recorded from the hippocampus in response to peripheral and mesencephalic reticular stimulation (GREEN and ARDUINI 1954). Recently GRASTYÁN et al. (1959), working with chronically implanted electrodes in cats, have shown that this slow rhythmic activity of the hippocampus is an invariable concomitant of the searching or orienting behavior following external sensory stimulation. In the light of the present findings this blocking of the hippocampal theta-activity by chlorpromazine thus possibly is an expression of the blocking of the attention or orienting response. Similarly, GLIEDMAN and GANTT (1956), working with dogs, recorded a complete elimination of the externally induced orienting reflex by 2.5 mg/kg of chlorpromazine.

Thus, it appears that an important effect of chlorpromazine is the blocking of the attention or orienting response and its concomitant electrical changes in the hippocampus (slow waves) as well as in neocortex (desynchronization). This is the case whether the response is produced by peripheral, cerebral cortical, intralaminar thalamic, or amygdaloid stimulation, whereas the arousal evoked by direct brain stem reticular excitation is less influenced by the drug.

According to the recent study by GRASTYÁN et al. (1959) the orienting (attention) response and the concomitant rhythmic slow wave activity of the hippocampus occur during the development of conditioned reflexes (defensive or alimentary). Since the attention response is blocked by low doses of chlorpromazine it might be expected that this compound might interfere also with conditioned reflexes. Indeed, there is ample evidence that this is the case. Thus, rats trained to climb or

jump to avoid an electric shock when a bell is sounded, fail to do so under the influence of chlorpromazine even though capable of responding to the shock (COURVOISIER et al. 1953; GUHA et al. 1954; BOWER et al. 1955; COURVOISIER 1956 b). The rat becomes disinterested in the bell ringing which no longer incites flight from pain. Such effects were not produced by barbiturates or morphine (COURVOISIER 1956 b). A similar indifference of chlorpromazine-treated animals to a stimulus conditioning a notion of pain has been reported by ADER and CLINK (1957), MILLER et al. (1957 a, b), RUTLEDGE and DOTY (1957), and ANOCHIN (1958). On the other hand, unconditioned avoidance reactions to noxious stimuli are not inhibited by chlorpromazine (BOWER et al. 1955; LEHMANN 1956). Also, conditioned salivatory reflexes are inhibited by low doses of chlorpromazine, 0,25—0,30 mg/kg i.v. (MALMÉJAC and PLANE 1955).

The site of action of chlorpromazine in the central nervous system still remains a matter of conjecture. The neuronal substrate of the attention or orienting reflex is not sufficiently known to allow any statement as to where the blocking of this reaction by chlorpromazine takes place. The response induced from the cerebral cortex and amygdala are probably mediated through the thalamic intralaminar nuclei and/or the brain stem reticular formation (JANSEN, ANDERSEN and KAADA 1955/56; URSIN and KAADA 1960 b). Whether the blocking occurs at the site of stimulation or at these subcortical areas cannot be resolved by the present experiments. However, it is known that the behavior attention reaction is also exhibited by decorticated animals (ROBINSON and GANTT 1947) and it appears likely that the blocking occurs at the subcortical areas mentioned. Pursuing the evidence brought forward by the microelectrode studies of BRADLEY (1957) that chlorpromazine possibly exerts a selective depression on the receptive side of the reticular formation, it might perhaps prove profitable to apply a similar hypothesis to explain the blocking of the same response when induced from the cerebral cortex and amygdala. The effect might be due to blocking of the cortical and amygdaloid influence on the reticular formation or the thalamus. It should be recalled that morphological data indicate a distinction between a lateral part of the reticular formation adapted to serve "receptive" and "associative" functions, and a medial region which seems to be more concerned with its "effector" functions. The latter are exerted rostrally ("ascending activating system") and caudally on the spinal cord (BRODAL 1957). A selective blocking at the "receptive" reticular neurons might explain the relative resistance to chlorpromazine of the behavioral arousal produced by direct medial reticular stimulation.

A subcortical site of action of chlorpromazine is also indicated by the studies of DASGUPTA et al. (1954) who showed that this drug suppressed sham rage in decorticate and diencephalic cats more efficiently than

affective behavior in normal animals. Similar behavioral changes produced by a pre-chiasmal lesion did not show such a hypersensitivity to chlorpromazine. Thus, a selective action of chlorpromazine also to apparently identical emotional reactions caused by lesions of different nervous structures is suggested.

According to LONGO (1956), chlorpromazine (doses not given) eliminates the fear and flight responses evoked by hypothalamic stimulation in rabbits. The failure to produce such an effect in the experiments described, even by doses causing overt signs of intoxication, is perhaps due to a similar selective action of this drug on various types of flight responses.

As to the clinical implications of the physiological data discussed, blocking of the attention response to sensory stimuli may explain the indifference to environmental and visceral stimuli and to pain in patients treated with chlorpromazine. However, it can hardly account for the relief of anxiety, agitation and tension, and for the reduced responsiveness to intrapsychic stimulation, such as to hallucinations; neither to the intrapsychic agitation with hyperactivity in manic states. It seems more reasonable to attribute the beneficial influence on these symptoms to a suppression of the nervous mechanisms responsible for the centrally induced attention reactions, in particular those elicited from the cerebral cortex.

The well-known lowering of the convulsive threshold in epileptics by chlorpromazine is similarly possibly related to the ability of this drug to block the attention response. It is a common clinical experience that sensory stimulation of various kinds in some patients may arrest seizure discharges.

Summary

1. The behavioral arousal associated with contralateral searching movements (the attention or orienting response) induced by cerebral cortical stimulation in unanesthetized cats was blocked by low doses of chlorpromazine (0.5 mg/kg i.p.) Amounts of 2 mg/kg, or more, were usually required to depress the similar response elicited from amygdaloid and intralaminar thalamic nuclei, whereas the threshold for the behavioral arousal evoked by midbrain reticular stimulation remained essentially unaltered with doses up to 10 mg/kg.

2. Behavioral arousal associated with fear (flight) or anger produced by posterior hypothalamic, thalamic, or midbrain reticular stimulation was almost unaltered at doses of 10 to 15 mg/kg of chlorpromazine.

3. It is concluded that chlorpromazine exerts a selective depressant action on certain behavioral arousal reactions. The arousal related to the attention (orienting) response evoked by cortical, intralaminar thalamic,

amygdaloid, and peripheral sensory stimulation is more susceptible to the drug than is the arousal associated with fear (flight) and anger elicited from the subcortical areas mentioned.

4. The clinical implications of the findings are briefly discussed.

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Chemistry and Pharmacology of Compounds Related to 4-(4-Hydroxy-4-Phenyl-Piperidino)-Butyrophenone

Part IV

Influence of Haloperidol (R 1625) and of Chlorpromazine on the Behaviour of Rats in an Unfamiliar "Open Field" Situation

By

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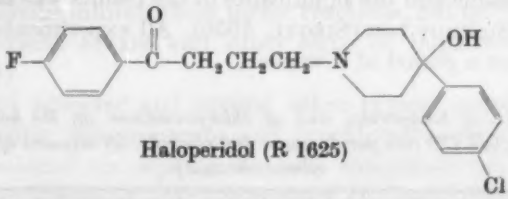
Previous papers of this series (JANSSEN et al., 1959a, b; 1960a) include several basic comparative pharmacological data on Haloperidol and Chlorpromazine.



Haloperidol (R 1625)

In mice both compounds were found to block righting and licking reflexes and to inhibit induced coordinated motility at comparable non-toxic dose levels of 0.5 to 5 mg/kg subcutaneously. Haloperidol however was shown to be much more active than chlorpromazine as a potentiator of pentobarbital in mice and as an antagonist of apomorphine emesis in dogs.

The purpose of this paper is to describe the influence of haloperidol and of chlorpromazine on exploratory motor activity and on emotional defaecation of rats in an unfamiliar "open field" situation.

Method

Subjects. Each experiment involves a group of five naive male inbred Wistar rats weighing from 200 to 250 grams and fed and watered ad libitum prior to the experiment.

Apparatus. The "open field" is an arena, made of black painted iron. Its diameter is 100 cm, its height 50 cm. Six grey diameters divide its bottom in six equal parts. A loud buzzer provides constant noise in the air conditioned laboratory ($22 \pm 2^{\circ}$ C; $65 \pm 15\%$ relative humidity). The only source of light in the room is a 150 Watt bulb, attached some 50 cm above the bottom of the arena and illuminating its centre. The illuminated area has a diameter of about 30 cm. A black screen (180×50 cm;

65° horizontal inclination) separates the observer from the arena, the animal in the arena being observed through a 5×50 cm aperture.

Design of the experiment. Five rats are given, at intervals of 4 minutes, a subcutaneous injection of haloperidol, chlorpromazine or saline (10 ml per kg) and put in individual plastic containers. 30 minutes thereafter the observer gently places each rat (same order; 4 min. intervals) in the arena and observes its behaviour for 3 minutes. He counts the frequency of diameter crossings ("ambulation score") and of rearings ("rearing score"). The number of faecal boluses excreted over the observation period of 3 minutes yields the "defaecation score".

A similar procedure was briefly described by RYALL (1958).

Preening is another frequent behaviour phenomenon occurring in these experimental conditions. We were however unsuccessful in finding a suitable quantitative method of scoring it.

The behaviour of treated rats was compared with that of 100 controls treated with saline and the significance of the results was assessed by the Kolmogorov-Smirnov test (SIEGEL, 1956). All experiments (Table) were conducted over a period of 2 weeks.

Table. *Influence of haloperidol and of chlorpromazine on the behaviour of naive rats in an open field (20 rats per dose and 100 controls: 30 minutes after subcutaneous administration)*

Drug	mg/kg s. c.	Average scores		
		ambulation	rearing	defaecation
Haloperidol	0.01	21.9	6.1	1.7
	0.02	22.6	6.3	1.2
	0.04	11.8[1]	4.3	1.8
	0.08	8.7[1]	2.3[1]	1.6
	0.16	3.3[1]	1.0[1]	2.1
	0.31	4.4[1]	0.6[1]	0.95
	0.63	2.0[1]	0.3[1]	1.1
	1.25	0.45[1]	0.05[1]	0.7
	2.5	0.15[1]	0.05[1]	0.3[1]
Chlorpromazine	0.63	23.7	4.2	0.73
	1.25	19.7	8.9	1.1
	2.5	14.5[1]	5.0	0.95
	5	11.1[1]	3.3[1]	0.10[1]
	10	4.0[1]	1.9[1]	0.05[1]
Controls . . .	saline	26.7	5.8	1.4

[1] active doses ($P<0.01$): Kolmogorov-Smirnov test (SIEGEL, 1956).

Results

None of the subjects ventured into the illuminated centre of the arena (BROADHURST, 1958). Both ambulation and rearing decline in frequency with increasing doses of either drug (Table), haloperidol being about

50 to 100 times more potent than chlorpromazine in this respect. The minimal active[1] doses for reducing ambulation of the geometric series used were resp. 0.04 and 2.5 mg/kg, as measured 30 minutes after dosage. Four hours after dosage comparable results were obtained, both compounds being long acting (JANSSEN et al., 1960a, unpublished results). Haloperidol however is only slightly more active than chlorpromazine in depressing defaecation in this open field situation (Table), the minimal active[1] doses being resp. 2.5 and 5 mg/kg.

Discussion

Ambulation and rearing of rats in an unfamiliar environment may be regarded as expressions of exploratory behaviour or coordinated motor reactions to environmental stress (RYALL, 1958; BROADHURST, 1958).

This interpretative terminology is supported by the fact that ambulation and rearing scores decrease in familiar environment (unpublished results).

Chlorpromazine inhibits these motor reactions, but only at dose levels producing obvious ataxia and other signs of impaired coordination (RYALL, 1958).

Haloperidol however and several other typical neuroleptic agents like perphenazine, thiopropazate and prochlorperazine (RYALL, 1958; unpublished results) are capable of nearly completely inhibiting ambulation and rearing without producing ataxia. A similar effect is observed in the human being, loss of slightly motivated coordinated motor activity, such as lack of mimic or monotony of facial expression, being regularly seen in psychotic patients under chronic haloperidol treatment at daily dose levels of 0.02 to 0.08 mg/kg (DIVRY et al., 1958; DIVRY et al., 1959; PAQUAY et al., 1959; FLEGEL et al., 1959; JACOBS, 1959; BOISSIER et al., in the press).

The average defaecation rate of a rat in an unfamiliar environment is from 10 to 30 times higher than the average daily rate (JANSSEN et al., 1959a). Anxiety motivated emotional defaecation is the interpretative terminology used by RYALL (1958) and BROADHURST (1958). The inhibition of this phenomenon by chlorpromazine and by haloperidol is not due to a peripheral constipating effect, although both drugs to produce constipation at higher dose levels (RYALL, 1958; unpublished results).

Summary

Haloperidol (R 1625) is 50 to 100 times more active than chlorpromazine as an inhibitor of exploratory motor behaviour in rats. Emotional defaecation in rats is inhibited by both drugs at similar dose levels.

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[1] $P < 0.01$

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Effects of Chlorpromazine upon Psychological Development in the Puppy*

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With 2 Figures in the Text

(Received November 30, 1959)

Interest has been expressed in possible deleterious residual effects of psychopharmacological agents, particularly when they are administered to children in phases of rapid psychological development. To our knowledge, no experimental studies designed to demonstrate the existence of such residual effects have been reported, and this experiment was conducted to fill the gap. Chlorpromazine was selected for particular attention because it is one of the most widely used tranquillizing drugs and its pharmacological and behavioral effects have been extensively described.

One might hypothesize that a naive organism whose early experience was obtained during chlorpromazine tranquillization would show effects similar to those produced by early sensory and social deprivation (FISHER 1955, MELZACK 1954, THOMPSON and HERON 1954a, b). This hypothesis carries the implicit assumption that "tranquillization" lowers the value of experience—that stimuli are less "meaningful" to a drugged animal, and that the organization of adaptive behavior patterns is more or less permanently impaired.

Because of the difficulties inherent in maintaining experimental subjects under continuous tranquillization over a prolonged period, we adopted a procedure of semi-isolation to restrict and control experience while providing stimulation adequate for essentially normal behavioral development. Puppies were reared mainly in isolation as soon as they were old enough to survive without regular maternal care. They were removed for short periods at regular intervals and subjected to highly standardized treatment and observation. The nature and duration of the training had been found in pilot studies to permit development of well-integrated adjustive behavior patterns to people, other puppies, and play objects. Experimental subjects received chlorpromazine before each training period, and an equal number of controls received no drug.

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If tranquillization does interfere with psychological development, we expected to find progressive behavioral deficits in the treated subjects.

Previous pilot studies to be reported elsewhere had established the fact that puppies isolated in this fashion, and not brought out at intervals, did differ markedly in behavior from semi-isolated controls. Although no specific quantitative prediction was made, we anticipated that the behavior of drugged semi-isolates would be intermediate between semi-isolates and complete isolates. However, the only hypothesis tested in this experiment was the prediction that drugged semi-isolates would differ from non-drugged semi-isolates.

As a further refinement, drugged and non-drugged subjects were separated into punished and non-punished groups to see if chlorpromazine had differential effects in a generally rewarding situation and in one designed to be aversive and anxiety-producing. The conjecture, in this instance, was that any effects of chlorpromazine would be greater in the punished groups.

Finally, in order to maximize the probability of obtaining significant effects from the drug treatment, we interposed a period of complete isolation between removal from the mother and the training-observation sessions. Delayed socialization has been reported to be less efficient than earlier training (SCOTT 1958). By starting the training of all puppies under the handicap of preliminary isolation, we hoped to produce greater vulnerability to the drug effects. Previous pilot studies had shown that control puppies reared under similarly scheduled life-histories were able to recover from the effects of short periods of complete isolation. We hypothesized that chlorpromazine would interfere with this readjustment.

Design of Experiment

Subjects were 32 beagle puppies from eight litters reared at the Jackson Memorial Laboratory. Four subjects were selected from each litter of more than four by random assignment. Puppies lived with their mother for three weeks and were placed in isolation at age 21 to 23 days, the exact date depending upon evaluation of their ability to feed themselves. Before isolation they were wormed and treated for external parasites.

Isolation cages 30 in. $\times$ 24 in. $\times$ 24 in. were constructed of plywood bolted to aluminum frames. Each cage was continuously illuminated by means of a flush-mounted unit in the door. A blower mounted on the door provided ventilation and also served to mask external sound. A floor of expanded metal mesh allowed urine and feces to drop into a pan of sawdust which could be removed periodically without touching the animals or allowing them to see the caretaker. A one-way-vision

window covered on the inside by a slide permitted the experimenters to inspect the dogs periodically. Food and water were introduced in stainless steel pans clamped to a long-handled carrier. A small hinged door in the top of the cage door allowed introduction of the food containers which were then lowered to the floor of the living compartment, the handle riding in a slot cut in the door. A curtain fastened above the food door concealed the experimenters from the subject during the introduction and removal of the food and water dishes.

The design of the experiment is set forth in Table 1. Subjects remained in a complete isolation through weeks four to seven. At the

Table 1. *Design of experiment*

Group	Weeks of age				
	1—3	5—7	8—11	12—15	16—17
A	with mother	complete isolation	CPZ no punish	CPZ-Litters 1, 3, 5, 7 no drug 2, 4, 6, 8 punish	All groups given runway test. No differential treatment
B			no drug no punish	CPZ-Litters 2, 4, 6, 8 no drug 1, 3, 5, 7 punish	
C			CPZ punish	CPZ-Litters 1, 3, 5, 7 no drug 2, 4, 6, 8 no punish	
D			no drug punish	CPZ-Litters 2, 4, 6, 8 no drug 1, 3, 5, 7 no punish	
			Phase I	Phase II	Phase III
	pre-treatment		arena tests semi-isolation		group living

CPZ indicates oral administration of chlorpromazine, 20 mg/kg, one hour before arena tests. Punish indicates that some objects in the arena were electrified, and subjects were struck when approaching the handler under certain conditions.

beginning of the eighth week the members of each litter were randomly assigned to four groups, A, B, C, and D. Half of the subjects were assigned to drug treatment which consisted of 20 mg. per kg. of chlorpromazine* given orally two hours prior to the arena tests which

* Chlorpromazine was generously furnished by Smith, Kline & French in the form of Thorazine Spansules. In this form, the chlorpromazine is liberated gradually.

are described below. One-half of the drug group (C) was assigned to a "punished" treatment, which involved training to avoid electrified objects and punishment by a handler for approaching at particular phases of the arena test. The other half (A) were assigned to a "non-punished" treatment. The control no-drug group was likewise subdivided into punished (D) and non-punished (B) subgroups. Arena tests were given five days a week for all subjects. This procedure was continued for four weeks, so that each subject during Phase I received a total of 20 training sessions approximately 15 minutes in length.

Phase II (12—15 weeks). All subjects on the "non-punished" procedure were changed to "punished", and the "punished" group was also reversed. For the odd-numbered litters, drug treatment continued as in the 8—11 week period. For even-numbered litters, drug treatment was reversed also. This second phase of the experiment also included 20 arena tests. Immediately following the last (fortieth) training period, the members of a litter were placed together in living pens approximately 6 ft. $\times$ 6 ft. No further drug treatment was given.

For the next two weeks (Phase III) additional observations on emotional and social behavior were made. Some of these tests were carried out in a new situation in order to test for generalization of treatment effects to a new situation. In addition, subjects were returned three times to the arena for repetition of the standard training procedures.

Experimental Procedures and Methods of Observation

The arena in which training and observation were carried out was fenced in by opaque barriers three feet high, enclosing an area 10 $^1/_2$ ft. $\times$ 10$^1/_2$ ft. divided into nine equal squares by white lines painted on the floor. Illumination was provided from windows and by an overhead light bulb. On three sides the fence was lined with poultry mesh which, for the "punished" puppies, could be electrified by means of an electric fence charger. A chair and a box with a ramp were present at all times in the arena. The top of the box was covered with wire mesh which could be electrified for the "punished" puppies. Stimulus objects could be lowered from the ceiling by means of pulleys. The arena test consisted of three parts designed to evaluate the subject's response to a human handler, to play objects, and to a littermate companion. Each part was further divided into two or more episodes which are described below. Observations were recorded continuously, except as noted, by an observer seated just outside the arena. The details of arena procedure are outlined below.

1. Hold: The handler carried the puppy into the arena, sat down in the chair, while stroking and speaking to the puppy which was

held in his lap for one minute. Following this, the handler sat quietly for an additional minute, restraining the puppy only enough to prevent his jumping to the floor. Observations were taken only during the second minute.

2. Sit: The puppy was placed on the floor while the handler remained seated and passive for one minute.

3. Walk: The handler walked slowly around the periphery of the arena for one minute, reversing directions each 20 seconds.

4. Crouch Active: The handler crouched for one minute in one corner of the arena and played actively with the puppy whenever it entered the corner square.

5. Crouch Passive: The handler remained in the same position for one minute, but made no response to the puppy.

6. Call: The observer from outside the arena extended his hand and called "Come". If the puppy did not approach and make contact, the word was repeated three times at 5-second intervals, making a total of 20 seconds allowed for response. The handler then called from his crouching position on the same time schedule. Finally, the observer again called the puppy. If the puppy made contact with the person calling, he was stroked and spoken to for the remainder of the 20-second period. At the end of this episode the handler left the arena.

7. Ball: With the use of a 5-ft. "stimulus presenter" a rubber ball 2 in. in diameter was dropped in front of the puppy and observations were recorded for two minutes.

8. Bell: A rubber dumbbell, with a metal insert which tinkled when shaken, was lowered from the ceiling and moved up and down to attract subject's attention. Stainless steel wire which could be electrified for the "punished" subjects was wound about the bell. Observations were made for two minutes.

9. Companion: Pairings for the companion episodes were always A with B and C with D within litters. The ball was removed, the bell raised, and the companion introduced in the center of the arena. Behavior was observed alternately for the first puppy in the arena and for his companion, one minute apiece.

10. Competition: A towel was lowered from the ceiling to furnish the puppies an opportunity to compete for its possession and control. Observations were continued for two minutes. Following the Competition period, the puppy which had been tested with the handler and play objects was removed and the companion was observed on the episodes with toys and handler. Members of a pair were regularly alternated between the first and second positions.

11. Punishment: The procedure for punished puppies was exactly the same as for the non-punished puppies, with the following exceptions:

The sides of the arena, top of the box, bell, and towel were electrified approximately once per second throughout the test period. In the Sit and Crouch-Active episodes, the handler punished the puppy by striking him with a rolled-up newspaper whenever the subject entered the square in which the handler was seated or crouched.

Behavior during the arena test was reported by a system of *sequential categorized activity time sampling* (SCATS). In this method, each minute is divided into twelve 5-second observation periods (Fig. 1).

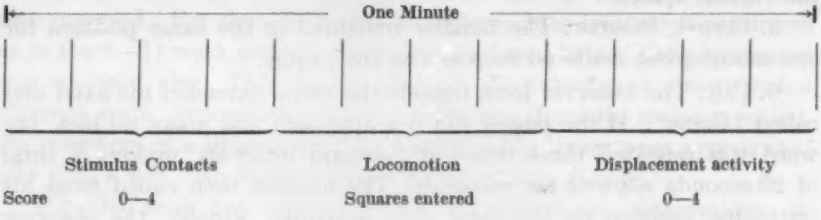

Fig. 1. Scheme of observation procedures for sequential categorized activity time sampling (SCATS)

During the first sequence of four observation periods, records were made of the contacts of the subject with the major stimulus present during each episode. A score of one was assigned for each 5-second period during which such contact is made. Thus, if a subject held the ball in his mouth continuously for 20 seconds he would receive a score of four, and if he touched it briefly at the sixth and eighteenth seconds, he would receive a score of two. Locomotor activity, measured by the number of squares entered, was recorded during the next sequence of observation periods. In addition, the observer rated general activity on a four point scale ranging from quiescence to vigorous activity. The remaining sequence of four 5-second periods was devoted to recording a variety of behaviors including vocalization, investigation, and orientation to the different features of the arena. Particular attention in our analysis of results has been given to responses to stimuli other than the handler, play objects, and companion, as recorded in the third time sample. We have called these "displacement activities" in that they were particularly liable to occur when the animal was frustrated in manipulating or relating to the primary stimuli in the experimental setting. We are not certain whether they correspond to displacement phenomena described in goal-frustrated animals by European ethologists or the familiar defense of displacement used to explain certain neurotic behaviors in humans.

A Runway Test was devised to measure the response of the animals to a reward which consisted of brief stroking by an experimenter. A runway, 16 ft. long × 4 ft. wide, was constructed, with opaque sides of black building paper. A starting compartment at one end could be closed off by a swinging door operated by an experimenter standing behind a screen. Subjects during testing were fitted with a harness to which could be fastened a snap lead running to an overhead trolley. Thus the subject was free to run, but he could be led in either direction without direct contact. At the far end of the runway was a screen behind which a second experimenter was seated, with arms extended into the runway through openings in the screen. Running time was taken as the interval between the opening of the starting gate and contact of the subject with the experimenter's hand. Following such contact, the dog was stroked gently for 10 seconds and was then led back to the starting compartment. One day was allowed for habituation to the apparatus and for observations of emotional behavior and resistance to being led. Beginning on the second day, subjects were run 10 trials daily for three days. If the subject failed to make contact with the experimenter's hands within two minutes, he was returned to the starting box and a new trial commenced.

Three variations of the simple runway problem were employed. On day 5, a wire barrier which obstructed the middle two-thirds of the runway was placed midway between the starting chamber and the goal. Ten trials were given under these conditions. On days 6 and 7 a group dominance test was carried out in the runway. The four puppies of the litter were placed, without harnesses, together in the starting box. Following the first heat, the winners was removed and a second heat was run with the three remaining subjects. The winner of this heat was removed and a third trial run between the two remaining subjects. Four sets of three heats were run on each of two days, thus providing eight ordinal rankings of dominance. Finally, all subjects were tested individually for "irrational fears". A doorbell mounted above the middle of the runway was sounded simultaneously with the opening of the starting gate on each trial. The bell was sounded for 10 seconds, or until subject made contact with the goal. Interposed with the runway tests were additional observations in the arena.

Results

It is convenient to present separately the results of the three phases of experimental treatment. During weeks 8—11 we were primarily interested in the differential effects of chlorpromazine and punishment upon the frequency of various responses and the age at which they first appeared. The second phase (weeks 12—15) was planned parti-

cularly to evaluate the effects of chlorpromazine upon the extinction of the avoidance responses learned by the two groups punished during Phase I. Finally, in Phase III, we compared the performance in a new situation of subjects who received chlorpromazine for eight, four (early and late), and no weeks, thus providing a measure of persistent behavioral effects.

No differences between groups in growth rate or other indicators of physical health were found at any time. In general, the wellbeing of the subjects compared favorably with that of puppies reared with their mother to normal weaning age.

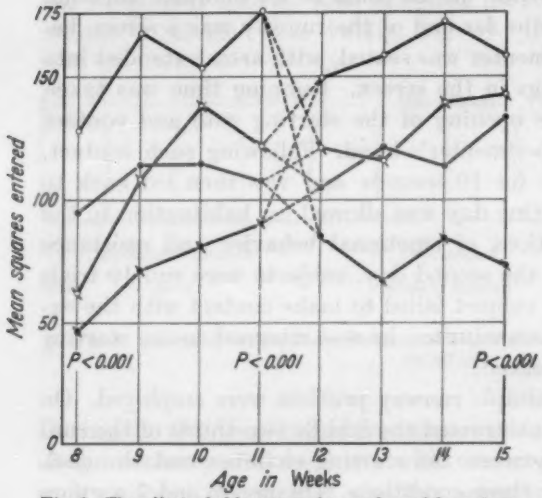

Fig. 2. The effect of chlorpromazine and punishment on locomotion. The treatment of each group is identified: Solid circles = chlorpromazine, 20 mg/kg; clear circles = no drug. A slash through the circle indicates punishment. Between weeks 11 and 12, subjects were shifted to new treatments as shown by the broken lines. Since the subgroups derived from different treatments during Phase I did not differ in Phase II, they were combined into four new treatment groups. The significance of the group differences at 8, 12, and 15 weeks of age is indicated

Phase I, Weeks 8—11. The mean locomotion scores for each experimental group are shown in the left hand side of Fig. 2. The differences between treatments were tested for significance in this and other comparisons by the Freedmann rank order analysis of variance (SIEGEL 1956). Throughout the four weeks non-punished, non-drugged dogs (Group B) were consistently highest in locomotion and punished, drugged dogs (Group C) were lowest. Groups A and D after the first week were approximately equal in locomotion. Group differences were significant at the 0.001 level. Both punishment and chlorpromazine decrease activity and they appear to act additively.

The mean number of stimulus contacts with the handler, ball, and companion are set forth in Table 2. During the eighth week (first week of treatment) group differences in contacts with the handler were significant ($p = 0.01$) and tended to be correlated with locomotion. By the eleventh week group differences had decreased and were non-significant. Ball contacts showed a similar trend, but Group D pups were significantly lower throughout. Contacts with the companion, on the other hand, were essentially equal for all groups and seemed to bear no relationship to differences in locomotion.

Table 2. *Mean stimulus contacts during weeks 8—11*

Stimulus	Group	CPZ	PUN	Week 8	9	10	11
Handler . . .	A	+	−	27.2	33.5	36.8	42.5
	B	−	−	27.2	38.3	42.7	44.5
	C	+	+	18,3	27.0	32.7	39.5
	D	−	+	22,3	31.8	40.5	44.6
Ball	A	+	−	10,0	18.7	22.2	23.1
	B	−	−	12.0	24.8	28.6	30.2
	C	+	+	10.2	10.1	17.2	23.5
	D	−	+	3.7	7.7	11.1	14.3
Companion . .	A	+	−	22.1	23.0	26.8	29.0
	B	−	−	21.6	27.6	29.8	29.5
	C	+	+	21.8	23.7	27.0	29.0
	D	−	+	21.7	28.8	31.1	32.6

Another measure of response to the handler was the number of times the subject was called before making contact ("come refusals"). During week 8 of the experiment, punished animals approached significantly less frequently than did non-punished. The effect persisted during the ninth week, but by the eleventh week the slight difference in approach was between drugged and non-drugged groups rather than punished and non-punished groups. Motivation to approach the handler was not reduced by punishment in other phases of the Arena Test, and the slower approach of the drugged animals was probably related to decreased attention.

Table 3. *Mean vocalization score for weeks 8—11*

Group	CPZ	PUN	Week 8	9	10	11
A	+	0	66.7	46.6	32.5	23.1
B	0	0	15.3	6.7	10.0	7.3
C	+	+	48.5	38.3	33.5	26.0
D	0	+	26.5	15.3	9.0	10.0

Displacement behavior has been summarized in two measures. Vocalization scored are presented in Table 3. Individual variation was so great that the differences did not reach statistical significance, but it is interesting that the subjects receiving chlorpromazine consistently vocalized more than their controls. Punishment appeared to have no effect. This finding was rather unexpected, since some investigators have used vocalization as an indicator of "anxiety", and one would have expected punished animals to be more "anxious" in the test situation.

A second measure of displacement behavior was the amount of investigation of safe features of the environment, chiefly the floor and the handler's chair (Table 4). Group differences were not significant during the first week, but significant changes ($p=0.02$) were found in

the trends of the four groups. Punished subjects increased their "save-investigation" scores. Non-punished animals, though more active, decreased their overall "safe-investigation". Drug treatment did not modify these relationships. All puppies appeared to carry out a certain amount of investigation when introduced to a stimulating environment. Subjects punished for approaching some of the more salient features of the environment ceased investigation of these areas, and concentrated upon other areas and objects. Punished puppies were often observed spending long periods sniffing and manipulating small pieces of dirt which were accidentally left on the floor.

Table 4. *Mean investigation of "safe environment" score, weeks 8—11*

Group	CPZ	PUN	Week			
			8	9	10	11
A	+	0	33.6	30.8	24.5	29.7
B	0	0	40.5	29.0	27.7	25.5
C	+	+	25.1	46.8	41.2	36.8
D	0	+	33.6	51.5	51.1	53.6

Groups C and D were compared with respect to the number of punishments that they received, to determine whether chlorpromazine impaired the ability to discriminate "safe" and "dangerous" situations. For the first three weeks the average number of shocks and swats was almost identical for the two groups. During the last week, there was a noticeable tendency for the C (chlorpromazine) group to receive more shocks than the non-drugged controls. Although this difference was significant by the signs test ($p=0.008$) it is not corroborated by other measures.

Another measure of the difference between the two punished groups is the time required to reach a criterion of no shocks, or no swats, for one session and for two consecutive sessions. This data, summarized in Table 5, showed no significant differences between the groups, although the direction of the difference in every comparison showed more rapid acquisition by the non-drugged puppies.

Table 5. *Measures of avoidance learning, weeks 8—11*

	Group means	
	C (CPZ)	D (no drug)
First shock-free day .	3.5	3.0
Two consecutive shock-free days . .	8.6	6.4
First swat-free day . .	6.1	4.0
Two consecutive swat-free days . . .	14.3	11.0

It may be argued that the more active non-drugged puppies have actually learned better, since part of the reduction in punishment of the drugged group can be attributed to reduced locomotion. The drugged puppies do not expose themselves to an equal risk, yet they receive approximately the same

amount of punishment overall. Even if this argument is accepted, the differences between the two groups with respect to learning to discriminate safe from dangerous situations appeared to be minor.

The four groups were also compared with respect to the time of first occurrence of certain responses. These results are summarized in Table 6. Punished subjects were slower to make contact with the handler and observer during so-called "safe" episodes. No differences attributable to chlorpromazine were found. In a number of instances, animals given chlorpromazine actually showed certain responses earlier than their controls. We may safely conclude that chlorpromazine in the dosages employed had no retarding effect upon the appearance of new response patterns.

Table 6. *First day for appearance of particular behavior incidents*

	Group mean			
	A (CPZ, —)	B (—, —)	C (CPZ, PUN)	D (—, PUN)
Contact with companion . .	1.1	1.5	1.1	1.4
Contact with bell.	1.4	1.7	2.6	4.4
Contact with ball	1.5	2.2	2.1	3.1
Contact during walk	1.9	1.9	4.2	4.4
Contact—handler's call . . .	2.5	2.6	5.0	8.0

In summary, the most striking difference between groups in Phase I was seen in locomotor activity. Certain other differ nces, such as those in number of contacts with the handler and with play objects, appear to be derivatives of this major effect. However, neither chlorpromazine nor punishment had much effect upon contacts with a companion puppy. Even before the quantitative estimates were available, the observers became aware of the fact that differences between drugged and non-drugged puppies were most apparent during the episodes with inanimate objects. In the companion period, both subjects were generally highly active and often appeared indistinguishable. Chlorpromazine may be said to have a major or a minor effect upon behavior, depending upon the nature of the eliciting stimulus complex.

Phase II, Weeks 12—15. The change from the non-punished to the punished condition elicited considerable disturbance in Group A and B subjects who had learned to play actively with the ball, jump against the wire barrier, and contact the handler frequently while he was seated or crouched. The subjects quickly discriminated between the safe and dangerous conditions in the arena. Although they received a little more punishment on the average during week 12 than did Groups C and D during week 8, the differences were not significant. The older pups did learn to avoid punishment more consistently ($p = <0.05$), but there was no difference between drugged and non-drugged groups.

Effects on locomotor activity were striking (Fig. 2). The locomotion curves for the four treatment groups during weeks 12—15 appear to be simple continuations of the 8—11 week curves, but it must be remembered that all subjects were shifted with respect to punishment, and half were changed with respect to drug. Thus each of the continuation groups was made up from an entirely different set of subjects. A rank order comparison within the 12—15 week treatment groups showed no differences attributable to the earlier treatment. Locomotor behavior appeared to be controlled by the immediate circumstances.

In general, subjects adapted from the non-punished to punished regime within a few days. Contacts with the handler during safe periods, with play objects, and with the companion, were maintained at the former level, indicating that punishment did not generalize from one episode to another.

The effects of the change from punishment to non-punishment were more interesting. The results set forth in Table 7 support the hypothesis that chlorpromazine would facilitate the extinction of the avoidance behavior acquired during weeks 8—11. The numbers of contacts with the handler (during crouch and sit) were little higher for the chlorpromazine group than for the non-drugged. Also fewer days elapsed before the chlorpromazine puppies made contacts with the handler or the bell. Whether drug was given or not during acquisition of the avoidance habit seems to be inconsequential. The significant fact is the nature of the treatment during the extinction phase.

Table 7. *The effects of chlorpromazine upon extinction of avoidance behavior acquired during weeks 8—11*

Group	Contacts with handler – sit and crouch		Contacts with bell		Contacts with previously electrified environment	
	Week					
	12	15	12	15	12	15
C odd, D even } CPZ	17.5	27.0	4.4	9.3	6.0	8.5
C even, D odd } no drug	7.0	28.0	2.0	10.4	1.3	9.7
p value	0.07	NS	NS	NS	0.07	NS

In summary, the results of Phase II confirm the facilitating effect of chlorpromazine upon the extinction of learned avoidance behavior. No deleterious effects were found upon learning a new avoidance pattern. Activity was decreased by punishment and drug treatment, the two agents acting additively.

Phase III, Post-treatment Tests. On the first day in the runway most subjects located the handler after a few trials and then ran readily.

Two subjects failed to run within the ten trials. The median of the average individual times was 7.3 sec.; the range from 4.3 sec. to 65.6 sec. (excluding the two who did not run). The median individual average time for the third day trials was 3.4 sec.; the range 2.2 sec. to 120.0 sec. (42.0 sec. excluding one subject who still failled to run). It is interesting to note that the running response can be acquired and maintained by a reinforcement procedure consisting of a few seconds of stroking. Although extinction trials were not run on these subjects, other experiments have shown that the running response disappears if the stroking is discontinued.

Placing the barrier in the runway increased running times (median increase 8.5 sec.), but no differential effects of treatment were found. Similarly the sounding of the bell had a temporary effect (median time for the first five trials 6.6 sec. as compared with 3.4 at the end of the training), but again no differences between groups were observed. Many subjects eventually ran faster during the bell ringing. The median average time for the last five trials was 3.0 sec., range 2.1—28.4 (excluding the non-running subject). Thus none of the individual runway measures discriminated between the treatments.

Table 8. *Effect of early treatment (8—11 weeks) upon runway dominance at 17 weeks*

Litter	Group			
	A	B	C	D
1	3	2	1	4
2	1	4	2	3
3	1	2	3	4
4	2	4	1	3
5	4	2	1	3
6	1	3	2	4
7	2	1	4	3
8	3	1	2	4
Sum	17	19	16	28
$\chi^2 = 6.76$	$p = < 0.10$			

Data on the runway dominance test are presented in Table 8. When classified according to the 8—11 weeks treatments, there is a hint that the D animals (non-drugged, punished) may be more subordinate, but the Freedman rank test does not reach the 0.05 level of significance. When the grouping is made according to the 12—15 weeks treatments, even this vestige of a difference disappears. Chlorpromazine treatment for either eight weeks or four weeks does not impair the ability of a pup to compete with its littermates when the drug is discontinued.

In summary, none of the post-treatment tests clearly discriminated the effects of chlorpromazine or of punishment. We conclude that, under the circumstances of our experiments, their effects are transitory.

Discussion

The major hypothesis with which this experiment started received no confirmation from the data. The effects of chlorpromazine upon psychological development appear to be minor, if in fact they exist

at all. This may be reassuring to those concerned about the occurrence of learning deficits or other impairments in children chronically treated with chlorpromazine. Yet our failure to demonstrate effects from tranquillization comparable to those of isolation does not mean that drugs cannot modify psychological development. One possibility is that chlorpromazine is a less effective inhibitor of learning than are some other drugs. HESS (1957), for example, has shown that meprobamate interferes with imprinting in ducklings, but chlorpromazine is ineffective.

Another way of adding sensitivity to our tests might be to reduce the amount of time the subjects spend in the arena. Fifteen minutes a day, five days a week, may permit gross overlearning of the discriminations and responses which a puppy acquires in our test situation. Under such circumstances, decrements in learning ability might not be detectable by our methods, particularly when puppies show such great individual variation.

The results of the study demonstrate that the amount of stimulation and opportunities to learn adaptive responses were fully adequate. Puppies in the arena situation were active, confident, and highly responsive to the test stimuli. Sufficient training was provided to permit organization of response systems even in the slowest subjects. Somewhere between 75 minutes per week and zero minutes per week is a minimal duration of exposure to complex stimulation necessary for the organization of social an manipulative response patterns. *Schedules of experience* may be as important in psychological development as schedules of reinforcement are in the rate of emission of particular responses.

It seems desirable to find critical schedules which provide the minimum experiential requirement in order to carry out more sensitive tests for drug effects on psychological development.

Summary

Puppies were removed from the mother at three weeks of age and isolated through the seventh week. During the 8th—11th weeks (Phase I) one half received chlorpromazine daily before being removed for a training and observation session in an open arena. One half of each group were always rewarded; the remainder were punished for certain forms of behavior.

During Phase II (weeks 12—15) all subjects were reversed on punishment, and half were reversed on drug. Observations in the arena were continued.

In Phase III (weeks 16—17) drug was withdrawn and tests were conducted in a runway and in the arena to measure persistent effects.

The results were as follows:

During Phase I, both drug and punishment depressed the activity level of the animals and did so additively. Chlorpromazine did not

impair the ability of the subjects to discriminate safe from dangerous situations in the Arena test and had no delaying effect upon the appearence of new responses; on the other hand, the drug did not alter the "anxieties" of the puppies in such a way as to enable them to enter new situations before non-drugged animals. Differences between drugged and non-drugged puppies were most evident in contacts with inanimate objects. In play with companion puppies, perhaps because of increased stimulus intensity, both groups were highly active and often indistinguishable. This would indicate the importance of stimulus context in interpreting behavioral effects from chlorpromazine.

In Phase II, in animals changed from a non-punished regime, it was again evident that chlorpromazine has no deleterious effects upon learning a new avoidance pattern; dangerous versus safe phases of the Arena test were readily discriminated. In groups changed from punishment to non-punishment, the facilitating effect of chlorpromazine on extinction of avoidance behavior was apparent. Whether or not drug had been given to the prior punishment phase was inconsequential; the crucial fact was the presence of drug treatment during extinction.

Phase III tests failed to demonstrate any significant differences between groups, either in arena behavior, willingness to run for handler contact, or in the runway dominance test.

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Reversible and Irreversible Dyskinesia after Treatment with Perphenazine, Chlorpromazine, Reserpine and Electroconvulsive Therapy*

By

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With 1 Figure in the Text

(Received March 5, 1960)

Neurological symptoms are often observed as side effects in the treatment of psychoses with psychopharmaca. Such neurological symptoms have hitherto been considered as a minor inconvenience because they disappeared after reduction of the dose or cessation of the treatment but now we have observed that neurological symptoms may persist as irreversible phenomena after cessation of the treatment.

The neurological symptoms which we have observed being irreversible in some cases is a syndrome (bucco-linguo-masticatory dyskinesia) consisting of incessant involuntary munching and masticatory movements of the jaw during which the tongue is protruded at short intervals with vigorous grimaces of the lips (see Fig. 1). In the most serious cases there are also rocking and torsionary body movements and incessant tripping and shuffling movements so that the patient can not stand still.

Shannon et al. (1957) have noted in patients treated with perphenazine occasional stiffness of the face and neck muscles together with protrusion of the tongue. The attacks disappeared after stopping perphenazine, reduction of the dose or administration of barbituric acid compounds.

Christian and Paulsen (1958) describe the case of a patient who was treated with small doses of prochlorperazine (Stemetil). On the third day of treatment an alarming state developed with protrusion of the tongue, spasms of the neck muscles, and later on opisthotonus and increasing respiratory trouble. Only intravenous injection of a barbituric acid preparation restored the patient.

Freyhan (1959) describes a "perioral" syndrome arisen under treatment with ataraxica consisting of involuntary protrusion of the tongue accompanied by tonic contraction of the muscles of the face and neck.

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Fig. 1. The various phases of a pronounced dyskinetic syndrome caused by chlorpromazine. (The squint is inborn)

These symptoms were observed in the first stage of the treatment. They disappeared after reduction of the dose and administration of kemadrine (procyclidine hydrochloride). Coffeic potassium benzoate was also effective.

DELAY et al. (1959) have given a comprehensive survey of various neurological symptoms after treatment with neuroleptica. They describe a number of types of dyskinesia as reversible phenomena, including bucco-linguo-masticatory crises, akathisia (difficulty of remaining in sitting position) and tasikinesia (a constant desire to walk).

The bucco-linguo-masticatory dyskinetic syndrome has thus been described more or less completely in the literature but so far only as reversible phenomenon.

In November and December 1957 we observed 2 cases of bucco-linguo-masticatory dyskinesia which arose as a direct result of electroconvulsive therapy. Dyskinesia is still present in these two patients, and is presumably due to some organic lesion.

During the winter and spring of 1959 we became aware of a number of similar syndromes that had developed in patients under pharmacotherapy and in June 1959 a systematical examination of all the about 500 patients of the department, who are all females, proved that a total number of 33 had this dyskinetic syndrome. 4 of these were ascribed to electroconvulsive therapy and 29 to treatment with perphenazine (Trilafon), chlorpromazine (Largactil), and reserpine (Serpasil). A number of the cases of dyskinesia caused by medicine have also proved irreversible. Observation of the patients was completed in October 1959.

15 of the 29 cases of dyskinesia ascribed to psychopharmaca are due to perphenazine (Trilafon), which often has a good effect on the psychic condition, but has proved to have many side effects when taken for some time. After the introduction of perphenazine for the treatment of psychoses a large number of cases of dyskinesia occurred simultaneously, and gradually we became aware of the fact that the dyskinetic syndrome was in some instances an irreversible result of pharmacotherapy with perphenazine.

We have treated altogether 155 patients with perphenazine. In 121 (78 per cent) there were side effects, which were more frequent in elderly patients than in the younger ones. Out of 98 patients under 60 years of age 73 per cent had side effects, and in 57 patients over 60 years of age 88 per cent had side effects. Most of these side effects were, however, slight and temporary. The symptoms in question were the same as described by other authors: rigidity, tremor, paresthesia, oculogyric crises, stridulous respiration, drowsiness, dryness of the mucous membranes, vertigo, and in a few cases nausea and vomiting.

Table 1 describes the 15 patients whose dyskinetic syndrome is ascribed to perphenazine. Most of the patients have taken other psychopharmaca before perphenazine, but only in moderate doses and for short periods, as will be seen from the table. Thus the other drugs have hardly had any important effect, and in 12 of the patients the syndrome arose during or immediately after the perphenazine treatment. It is characteristic of the dyskinesia due to perphenazine observed here that

Table 1. *15 patients with Dyskinetic syndrome after treatment with perphenazine*

Number and name	Age	Diagnosis and duration of disease	Treatment	Average dosis per 24 hours (mg)	Dyskinesia
1. H. K.	55	Schizophrenia. 6 years	1956/58 chlorpromazine for 20 months 1958 perphenazine for 1 month Treatment terminated December 1958	170 35	Dyskinesia observed in December 1958, disappeared 4 months after ceasing treatment
2. M. P.	63	Schizophrenia. 20 years	1958 perphenazine for 8 months Treatment terminated December 1958	28	Dyskinesia observed in November 1958, treatment terminated one month later, dyskinesia disappeared 3 months after ceasing treatment
3. A. C.	61	Schizophrenia (prefrontal leucotomy 1949 and releucotomy 1954). 33 years	1954/55 chlorpromazine for 7 months 1955/57 reserpine for 20 months 1957/58 chlorpromazine for 17 months 1958 perphenazine for 3 months 1958 chlorpromazine for 1 month 1959 perphenazine for $^1/_2$ month Treatment terminated February 1959	270 4.5 265 20 250 60	Tremor was observed during treatment with perphenazine in February 1959. Dyskinesia appeared 10 days after termination of treatment and persists still 8 months later
4. Eb. S.	62	Schizophrenia (severe icterus after chlorpromazine in 1955). 5 years	1955 2 ECT 1956 9 ECT 1956 reserpine for 1 month 1956/57 reserpine for 15 months 1958 perphenazine for 2 months Treatment terminated September 1958	 2 0.5 15	Dyskinesia observed September 1958, disappeared a few weeks after ceasing treatment
5. E. N.	75	Senile dementia. 5 years	1956/57 reserpine for 10 months 1958 perphenazine for 7 months Treatment terminated January 1959	1.5 17	Dyskinesia observed January 1959 persisting 9 months after ceasing treatment
6. L. A.	48	Schizophrenia (prefrontal leucotomy 1949) 30 years	1957 chlorpromazine for 1 month 1958 perphenazine for $2^1/_2$ months Treatment terminated October 1958	150 20	Dyskinesia observed October 1958, disappeared 2 weeks after ceasing treatment
7. L. F.	52	Schizophrenia. 25 years	1955 chlorpromazine for 7 months 1956 chlorpromazine for 9 months 1958/59 perphenazine for 6 months Treatment continues	225 350 40	Very slight degree of dyskinesia observed February 1959, disappeared after administration of brocadisipal and reduction of dose in spite of continuing perphenazine treatment
8. N. O.	64	Schizophrenia. 40 years	1955 chlorpromazine for 3 months 1955/56 reserpine for 11 months 1958 reserpine for $^1/_2$ month 1958/59 perphenazine for $3^1/_2$ months Treatment terminated February 1959	280 4 2.5 45	Dyskinesia observed February 1959, disappeared 4—6 weeks after ceasing treatment

Table 1 (continued)

Number and name	Age	Diagnosis and duration of disease	Treatment	Average dosis per 24 hours (mg)	Dyskinesia
9. G. H.	63	Dementia after meningoencephalitis (prefrontal leucotomy 1956 and relcucotomy 1959). 9 years	1952/53 22 ECT 1955 chlorpromazine for 1 month 1955/56 veserpine for 9 months 1956 14 ECT 1956/57 chlorpromazine for 15 months 1957/59 perphenazine for 16 months Treatment terminated March 1959	250 4.5 250 54	Dyskinesia observed in March 1959, 3 weeks after ceasing treatment, unaltered 7 months later, not influenced by leucotomy in July 1959
10. E. S.	60	Schizophrenia (prefrontal leucotomy 1959). c. 20 years	1957 11 ECT 1957 chlorpromazine for 1½ month 1957 reserpine for 3 months 1958 2 ECT 1958 reserpine for 2 months 1958 perphenazine for 8 months One month after termination of treatment with perphenacine the patient resumed treatment with reserpine in varying dosis. April 1959 18 ECT. September 1959 prefrontal leucotomy	300 5 10 60	Pronounced Parkinsonism occured during treatment with perphenazine, dyskinesia appeared shortly after ceasing this treatment and has since persisted
11. V. A.	63	General paralysis (malaria and penicillin treated). 5 years	1958 chlorpromazine for 1 month 1958 prochlorperazine (Stemetil) for 1 month 1958 chlorpromazine for 3 months 1958 perphenazine for 4 months 1959 reserpine for 4 months Continues treatment with reserpine	75 50 175 46 0.7	Dyskinesia observed in June 1959, persisting unaltered 4 months later
12. H. W.	82	Arteriosclerotic dementia. 2 years	1958 chlorpromazine for 1 month 1958/59 perphenazine for 6 months Treatment terminated May 1959	75 12	Dyskinesia observed in May 1959, persisting 5 months after ceasing treatment
13. A.M.J.	75	Schizophrenia. 52 years	1955 reserpine for 2 months 1958 chlorpromazine for 1 month 1958/59 perphenazine for 9 months Treatment terminated June 1959	3 125 8.5	Dyskinesia observed in June 1959, grimaces having, however, been observed for several years. The dyskinetic syndrome persists 4 months after termination of treatment
14. L.V.J.	53	Chronic epidemic encephalitis (Economo). 24 years	1956 chlorpromazine for 2 months 1957 chlorpromazine for½ month 1958 perphenazine for 6 months Treatment terminated January 1959	325 325 30	Dyskinesia observed in June 1959, persisting 9 months after ceasing treatment
15. J. M.	80	Senile dementia (hypertensive encephalopathy) 10 years	1959 perphenazine for 1½ month 1959 chlorpromazine for 1 week Treatment terminated April 1959	20 60	Dyskinesia observed in July 1959, persisting 6 months after ceasing treatment

it occurs late in the treatment period. It has at the earliest been observed on the 16th day of treatment. 5 of the patients did not show symptoms until the treatment had lasted for more than 200 days, one patient only after 482 days. In 3 patients (nos. 11, 14, and 15) the syndrome was only observed some time after the termination of the treatment, when the systematic review of all the patients in the department was carried out. We may have overlooked the syndrome in these patients at the time when the treatment with perphenazine was stopped for other reasons, but we have seen several cases of the dyskinetic syndrome becoming more pronounced or even appearing for the first time

Table 2. *10 patients with Dyskinetic syndrome after treatment with chlorpromazine*

Number and name	Age	Diagnosis and duration of disease	Treatment	Average dosis per 24 hours (mg)	Dyskinesia
1. A. O.	79	Senile dementia. 13 years	1956 chlorpromazine for 9 months 1957/59 chlorpromazine for 30 months Continues treatment	225 150	Dyskinesia observed since June 1959, persisting in October 1959
2. R. A.	70	Schizophrenia. 27 years	1956/59 chlorpromazine for 33 months Continues treatment	200	Dyskinesia observed since June 1959, persisting in October 1959
3. A. S.	71	Schizophrenia. 37 years	1956/57 chlorpromazine for 12 months Treatment terminated December 1957	150	Dyskinesia observed June 1956, still persisting in October 1959 22 months after termination of treatment
4. M. B.	76	Manic-depressive psychosis (lymphatic leucemia). 44 years	1955 chlorpromazine for 6 months 1956 chlorpromazine for 2 months 1957/58 chlorpromazine for 12 months 1959 chlorpromazine for 6 months Treatment terminated June 1959	200 225 275 250	Involuntary movements of the jaw observed since 1956. Fully developed dyskinetic syndrome observed in June 1959. The syndrome persists 4 months after cessation of treatment
5. M. F.	67	Dementia arteriosclerotica (emotional instability). 13 years	1955/56 chlorpromazine for 3 months 1957/59 chlorpromazine for 26 months Treatment terminated June 1959	150 200	Dyskinesia observed in June 1959, remains 4 months after termination of treatment
6. A.M.N.	53	Schizophrenia. 23 years	1955/56 chlorpromazine for 6 months 1956/59 chlorpromazine for 28 months Continues treatment	225 275	Dyskinesia observed June 1959, persisting in October 1959
7. E.M.J.	72	Senile dementia. 4 years	1955 3 ECT 1956 9 ECT 1956 chlorpromazine for 1 month 1956 reserpine for 2 months 1957 reserpine for 1 months 1957/59 chlorpromazine for 24 months Continues treatment	 225 4 5 175	Dyskinesia observed June 1959, persisting in October 1959
8. O. H.	77	Senile dementia. 5 years	1956 chlorpromazine for 1 months 1956 chlorpromazine for 4 months 1957 reserpine for 1 month 1957 reserpine for 2 months 1958/59 chlorpromazine for 18 months Continues treatment	75 50 2 1.5 100	Dyskinesia observed June 1959, persisting in October 1959
9. X. N.	54	Schizophrenia. 24 years	1955 reserpin for 2 months 1957/59 chlorpromazine for 18 months Continues treatment	5 150	Dyskinesia observed June 1959, persisting in October 1959
10. L. N.	52	Schizophrenia. 18 years	1956 reserpine for 1 month 1956/59 chlorpromazine for 39 months Continues treatment	1.5 250	Dyskinesia observed July 1959, persisting in October 195

when Parkinsonian rigidity caused by pharmaca diminished after reduction of the dose or termination of the treatment. In two patients (nos. 10 and 11) further treatment with reserpine was indicated, and in both cases dyskinesia still remains unabated. In no. 7 dykinesia disappeared on reduction of the dose of perphenazine.

Perphenazine treatment has terminated in 12 cases, and in 5 of these cases dyskinesia disappeared after a fortnight to 4 months, but in 7 patients dyskinesia still remains at the end of the observation period in

Table 3. *Patient with Dyskinetic syndrome after treatment with reserpine*

Name	Age	Diagnosis and duration of disease	Treatment	Average dose per 24 hours (mg)	Dyskinesia
O. P.	72	Schizophrenia. 27 years	1955/58 reserpine for 35 months 1958/59 reserpine for 10 months Continues treatment	2 3.5	Dyskinesia observed since June 1959 somewhat diminished under treatment with benztropine (Cogentine)

October 1959, respectively 4, 5, 6, 7, 8, 9, and 9 months after the cessation of perphenazine treatment.

Table 2 shows 10 patients in whom the dyskinetic syndrome is ascribed to chlorpromazine. 6 of these patients have not had any other psychopharmaca than chlorpromazine, while 4 have also had small doses of reserpine for short periods, but chlorpromazine treatment was of long duration and predominating in all 10 patients.

In 7 cases further chlorpromazine treatment was indicated in spite of dyskinesia, which still remains unchanged in these 7 patients. In 2 cases treatment ceased in June 1959 but dyskinesia was unchanged at the end of the observation period 4 months later.

No. 3 patient stopped chlorpromazine treatment in December 1957, but dyskinesia was not observed prior to the systematic examination of all patients in June 1959, and then only in a mild degree. As the patient has had no other treatment than chlorpromazine, it is however probable that dyskinesia has been present since the chlorpromazine treatment. The patient shows no sign of encephalitis or other plausible causes of the dyskinetic syndrome.

Table 3 shows one patient with a typical dyskinetic syndrome. The patient has had no other pharmacotherapy than reserpine, small doses being given for a long time. There are no other traceable causes of the dyskinesia, and we may thus presume that it was caused by the reserpine. The patient continues the reserpine treatment which has a good effect on the psychosis. Dyskinesia has diminished under treatment with Cogentine (Benztropine Methanesulfonate).

Table 4 lists 3 patients treated with various psychopharmaca. It is not possible to judge which substance is the principal cause of the syndrome. In no. 1 patient the syndrome disappeared on reduction of the thioridazine (Melleril) dosis. In no. 3 the dyskinesia disappeared in 4 months after the termination of the treatment, but in no. 2 dyskinesia has now persisted for 8 months after the termination of the treatment.

In Table 5 four patients are entered in whom the dyskinetic syndrome is ascribed to electroconvulsive therapy. In the two first cases dyskinesia arose in immediate connection with electroconvulsive therapy,

Table 4. *3 patients with Dyskinetic syndrome after treatment with various drugs*

Number and name	Age	Diagnosis and duration of disease	Treatment	Average dosis per 24 hours (mg)	Dyskinesia
1. H.A.P.	66	Dementia. Encephalopathia atrophicans. 9 years	1957 reserpine for 1 month 1958 chlorpromazine for 2 months 1958 perphenazine for 4 months 1959 thioridazine for 6 months Continues treatment with thioridazine in reduced dose	2 200 20 75	The dyskinetic syndrome which was observed in June 1959 was somewhat atypical, the rhythm being faster than usual. The syndrome disappeared 3 months after reduction of thioridazine dose
2. A. N.	78	Dementia arteriosclerotica. 5 years	1957 chlorpromazine for 7 months 1958 chlorpromazine for 3 months 1958 perphenazine for 1 month 1958/59 thioridazine for 3 months Treatment terminated February 1959	225 125 20 80	Dyskinesia observed in June 1959, still persisting 8 month after ceasing the treatment
3. K. N.	43	Schizophrenia. 20 years	1958 chlorpromazine for 2 months 1958 perphenazine for 6 months 1958/59 thioridazine for 8 months Treatment terminated June 1959	325 50 225	Dyskinesia observed in June 1959, disappeared in 4 months

Table 5. *4 patients with Dyskinetic syndrome after ECT*

Number and name	Age	Diagnosis and duration of disease	Treatment	Average dosis per 24 hours (mg)	Dyskinesia
1. G. P.	71	Manic-depressive psychosis (protracted endogenous depressions). 55 years	1952/54 20 ECT 1955/56 chlorpromazine for 13 months 1956/57 chlorpromazine for 3 months November 1957 12 ECT 1958 chlorpromazine for 7 months	 200 250 200	Dyskinesia arose in immediate connection with ECT in November 1957. The syndrome persisting 23 months later
2. A.H.N.	56	Schizophrenia (prefrontal leucotomy 1949). 15 years	1955/56 chlorpromazine for 16 months 1956 reserpine for 1 month 1957 chlorpromazine for 4 months 1957 chlorpromazine for 5 months December 1957 13 ECT	250 3 300 400	Dyskinesia arose in immediate connection with ECT in December 1957. It persists unchanged 22 months later
3. D. A.	74	Senile melancholia. 8 years	1952/59 a total of 192 ECT 1955 chlorpromazine for 3 months 1955 reserpine for 6 months 1956 chlorpromazine for 2 months 1956/57 reserpine for 1 month 1957 chlorpromazine for 1 month 1958 perphenazine for 1 month ECT treatment once a week continues	 250 3 200 3 200 16	Dyskinesia observed in April 1959, persisting unchanged since then
4. A.M.S.	72	Senile depression. 5 years	1955/58 28 ECT 1958 reserpine for 3 months 1958 chlorpromazine for 1 month April 1959 1 ECT May—July 1959 chlorpromazine for 2 months Chlorpromazine treatment terminated July 1959	 0.75 100 100	Dyskinesia observed in June 1959, has since abated considerably

which is thus undoubtedly the direct cause. Patient no. 3 has had pharmacotherapy for short periods with moderate doses of chlorpromazine, reserpine and perphenazine, but very intensive electroconvulsive

treatment, which treatment is the only one to have recognisable effect on the psychosis. In this patient electroconvulsive therapy is presumably the main cause of the dyskinetic syndrome. Patient no. 4 had so little pharmacotherapy that this can hardly have caused dyskinesia, thus electroconvulsive therapy is presumably the main cause. Dyskinesia dimished in this patient although chlorpromazine treatment continued for one month after the observation of the syndrome, but three months after the termination of the chlorpromazine treatment dyskinesia has, however, not yet completely gone.

Discussion

Out of 29 patients with dyskinesia caused by pharmacotherapy continuation of this therapy was indicated in 12 cases. In 2 of these 12 cases dyskinesia disappeared on reduction of the dose. In the 10 other patients who have continued pharmacotherapy dyskinesia still persists. In some instances dyskinesia has diminished after Cogentine treatment, while treatment with anti-Parkinson compounds such as Brocadisipal (β-dimethylaminoethyl-2-methylbenzhydryletherhydrochlorid) and Aturban was without recognisable effect.

17 patients have stopped pharmacotherapy, and in 6 of them dyskinesia disappeared within 10 days to 4 months after the cessation of the treatment. 5 of these 6 patients had had perphenazine and one patient had had various compounds.

In 11 of the 17 patients who terminated pharmacotherapy dyskinesia has remained after the termination of the pharmacotherapy. 7 of these cases were treated with perphenazine, and dyskinesia persists 4, 5, 6, 7, 8, 9, and 9 months respectively, after the treatment. This group also includes 3 patients treated with chlorpromazine, in whom dyskinesia has so far lasted 4, 4, and 22 months respectively, and one patient treated with various pharmaca in whom dyskinesia has lasted for 8 months. Some of these 11 cases of dyskinesia may disappear, but this is unlikely, since so far no patient shows any sign of improvement.

5 patients with permanent dyskinesia were aware of these involuntary movements, and two of them were much inconvenienced. The remaining patients with permanent syndromes are on account of their psychosis hardly aware of their dyskinesia; at least they do not complain of it. However, dyskinetic patients inevitably attract the attention of their surroundings, and thus these patients are also caused great inconvenience by their ailment.

It seems as if perphenazine is the most toxic of the pharmaca in question, as 15 cases of dyskinesia have been found, including 7 irreversible ones, amongst 155 patients treated with perphenazine.

The relatively large number of cases of dyskinesia caused by chlorpromazine (10, out of which 3 are irreversible) are due to the fact that chlorpromazine has been the chief drug of the department since 1954. Several hundred patients have been treated with chlorpromazine but it is not possible to give the exakt number.

Reserpine is only used as an exception, generally as an experiment when other treatment has no effect. Thus no conclusions may be drawn as to the toxidity of reserpine from the single case of dyskinesia due to reserpine.

Most of our cases of bucco-linguo-masticatory dyskinesia occurred after prolonged treatment while the reversible dyskinetic symptoms described in the literature occurred at an early stage of the treatment.

It should be noted that the patients in which the dyskinetic syndrome occurs are rather old, the average age being 66, and among the younger patients several have an organic brain disease. Therefore it may be presumed that the dyskinetic syndrome occurs most easily in elder persons and in persons with organic brain lesions.

We conclude from the present material that prolonged administration of psychopharmaca carries the risk of manifestation of bucco-linguo-masticatory dyskinesia which in some cases may prove to be irreversible. The risk of manifestation of a dyskinetic syndrome seems greatest in elderly patients and in persons with organic brain diseases[1].

Summary

A dyskinetic syndrome consisting of involuntary grimaces, mastication, and propulsion of the tongue, in some cases in connection with akathisia and tasikinesia, due to electroconvulsive therapy, has been observed in 4 patients.

Moreover 29 cases have been observed, which were due to pharmacotherapy, in 15 cases with perphenazine, 10 cases with chlorpromazine, and one case with reserpine, and in 3 cases with various compounds.

12 patients are continuing the pharmacotherapy and dyskinesia disappeared in 2 of these cases after the dose had been reduced.

17 patients discontinued the treatment, but in 11 of these dyskinesia proved irreversible after an observation period of 4 to 22 months.

[1] Renewed investigation in May 1960 of the 11 patients with "irreversible" bucco-linguo-masticatory dyskinesia showed: In 1 case the dyskinesia disappeared in 6—7 months, in 2 cases the pharmacotherapy was renewed because of the psychotic condition. 4 patients have died, they had all of them dyskinesia when they died 7, 10, 15 and 23 months after cessation of the treatment, in 3 of these cases the brain is undergoing histological investigation which has not yet been finished. 4 patients have still dyskinesia 11, 12, 13 and 16 months after cessation of the treatment respectively. In May 1960 we have further observed 3 cases of the dyskinetic syndrome due to thioridazine (Melleril).

Dyskinesia generally occurred after prolonged treatment in elderly patients and patients with organic brain diseases.

The conclusion is drawn that prolonged administration of psychopharmaca, which cause neurological side effects, carries the risk of lesion of the central nervous system with irreversible dyskinesia, especially in elderly patients and patients with organic brain diseases.

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Zur Testung depressiv auf das Zentralnervensystem wirkender Pharmaka

Von

M. Müller und J. Gebhard

Mit 1 Textabbildung

(Eingegangen am 5. Juli 1960)

Zur Charakterisierung der Effekte psychotroper Pharmaka haben sich neben neurophysiologischen Untersuchungsverfahren auch zahlreiche Methoden als zweckmäßig erwiesen, denen bestimmte stabile Leistungen von Versuchstieren zugrunde liegen. Derartige Untersuchungen führten gerade in den letzten Jahren zur Aufdeckung interessanter Beziehungen zwischen den Effekten einiger Pharmaka auf spezielle Verhaltensreaktionen des Tieres und den Wirkungen derselben Stoffe auf psychische Vorgänge des Menschen. Jedoch zeigten sich dabei auch die besonderen Schwierigkeiten in der Beurteilung pharmakologischer Wirkungen auf das Verhalten im Tierversuch (Miller und Barry, Sidman).

Die Mehrzahl der uns zugänglichen Untersuchungen über die Beeinflussung tierischer Leistungen durch Pharmaka ließ den Reaktionen des Tieres nur Spielraum im Sinne einer quantitativen Veränderung; als Beispiel sei die Registrierung der Reaktionszeit im bedingten Fluchtreflex der Ratte erwähnt. Solche Untersuchungen machen zudem Störungen der Koordination beim Versuchstier oft schlecht faßbar. Es ist dann schwierig zu entscheiden, ob die Substanz die spezielle getestete Leistung beeinflußte, oder ob dem Tier die Reaktion durch die Koordinationsstörung unmöglich wurde.

In unseren Arbeiten zur Entwicklung geeigneter Untersuchungsverfahren gingen wir davon aus, auf der Grundlage einer stabilen tierischen Leistung die Möglichkeit qualitativ verschiedener Reaktionen nach Applikation eines psychotropen Pharmakons offenzulassen und diese als Kriterien zu benutzen. Als einigermaßen geeignet erschien uns hierzu die Irrgartenmethode, die bekanntlich in der psychologischen Forschung eine erhebliche Rolle spielte und mit der auch einige pharmakologische Fragestellungen bearbeitet wurden. Während wir zunächst deutlich verschiedene Wirkungen zweier Tranquillisantien auf die Reaktionen der Ratte beobachten konnten (Kiesewetter und Müller), interessierte uns in der Folge die Frage, ob sich das Untersuchungsverfahren zur Differenzierung von Pharmaka aus der Gruppe der Hypnotica bzw.

Neuroleptica eignet und ob sich für Urethan und Phenyläthylbarbiturat einerseits und Chlorpromazin, Prothipendyl[1] und Reserpin andererseits, charakteristische Abweichungen ergeben würden.

Methodik

Der Irrgartenmethode dürften bedingt-reflektorische Abläufe zugrunde liegen. Nach DEMBOWSKI könnte es sich um die Prüfung eines komplexen bedingten Reflexes handeln, der sich im Verlaufe der Errichtung aus einer aufeinanderfolgenden Reihe verschiedener Reize aufbaut und bei dem schließlich die gesamte Situation den bedingten Reiz liefert. Die an den Ergebnissen dieser Methode seitens der psychologischen Forschung geknüpften Theorien halten einer genaueren Beurteilung vielfach nicht stand (PAWLOW). Für die pharmakologische Untersuchung nach diesem Verfahren ist die Stabilität der Leistung, ihre reproduzierbare Beeinflussung durch Pharmaka und der geringe zeitliche und materielle Aufwand das Wesentliche. Hinweise auf verschiedene Untersuchungen nach der Irrgartenmethode wurden in einer früheren Mitteilung (KIESEWETTER und MÜLLER) gegeben, die methodischen Einzelheiten entsprachen weitgehend den dort beschriebenen. Einiges sei hier wiederholt:

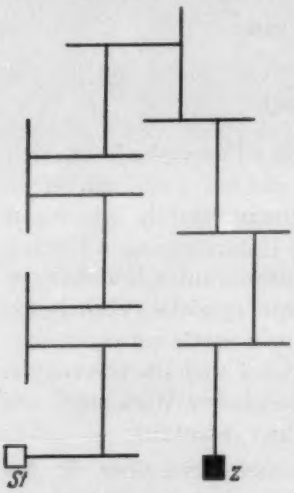

Abb. 1. Konfiguration des erhöhten Irrgartens. Länge der einzelnen Teilstücke 90 cm, Breite 2,5 cm *St* = Startplatz, *Z* = Ziel

a) Die Verwendung eines *erhöhten Irrgartens* erwies sich als zweckmäßig, weil aus naheliegenden Gründen durch Pharmaka bewirkte Koordinationsstörungen (Ausgleiten der Tiere) zahlenmäßig faßbar wurden. Die T-förmige Struktur des Labyrinths ist in der Abb. 1 ersichtlich; sie wich nicht prinzipiell von der in den früheren Untersuchungen verwendeten ab.

b) Die *Versuche* wurden an 100 etwa gleichaltrigen männlichen Albinoratten im Gewicht von 120—150 g (bei Versuchsbeginn) durchgeführt. Es handelte sich um Tiere eines Eigenzuchtstammes, deren reproduzierbare Leistung im verwendeten Untersuchungsverfahren in zahlreichen früheren Versuchen bestätigt werden konnte. Nach einer kurzen Gewöhnungsperiode lernten die Tiere bei täglich einem Trainingsversuch von Mal zu Mal größere Abschnitte des Irrgartens (vom Ziel aus betrachtet) kennen; am Ziel erhielten die Tiere eine Standardfutterration,

[1] Versuchsmengen von Prothipendyl (Dominal) wurden uns freundlicherweise von der Homburg AG., Frankfurt a. M., überlassen.

die den täglichen Nahrungsbedarf deckte. Nach der dreiwöchigen Trainingsperiode waren während weiterer zwei Wochen stabile Leistungskriterien erreicht, so daß die Testungen unter pharmakologischer Behandlung angeschlossen werden konnten. Während dieser Testperiode wurde gleichfalls von jedem Tier täglich einmaliges Durchlaufen des Labyrinths verlangt. Zur Überwachung des Nahrungsbedarfes wurde das Gewicht der Ratten regelmäßig kontrolliert; geringere Schwankungen in der Futtermenge hatten keine sicheren Abweichungen in den Leistungen der Tiere zur Folge. Futterprivation über 48 Std führte zu einer leichten Erhöhung der Laufgeschwindigkeit bei einzelnen Ratten, aber auch zu einer Vermehrung der Fehler und Halte (s. unter Abschnitt c), so daß die Leistungen an Zuverlässigkeit und Vergleichbarkeit einbüßten. Von einer Berücksichtigung der Futterprivation in den Testungen der Pharmaka wurde daher für die betreffende Fragestellung abgesehen, eine Bewertung der Geschwindigkeit der Nahrungsaufnahme wurde nicht vorgenommen.

Die Applikation der Substanzen erfolgte stets intraperitoneal. Näheres über die Variierung des zeitlichen Abstandes zwischen Injektion der Substanzen und Beginn der Testung ist im Ergebnisteil ersichtlich.

c) Wir registrierten (Beobachtung seitens der Experimentatoren) folgende *Leistungskriterien*:

1. Durchlaufzeit (Zeit vom Beginn des Laufes bis zum Erreichen des Zieles bzw. bei Nichterreichen maximal 5 min),

2. verschwendete Zeit (Zeit, die durch Laufen in Sackgassen bzw. zurück nach dem Startplatz oder durch Halte des Tieres verstrich),

3. Zahl der Fehler (Laufen in Sackgassen bzw. zum Startplatz hin entsprechend der Anzahl betroffener Teilstrecken),

4. Zahl der Halte,

5. Häufigkeit des Ausgleitens (Abrutschen von der Laufstrecke, meist mit den Hinterextremitäten).

d) Zur *statistischen Bearbeitung* der Versuchsergebnisse wurden je nach Eignung folgende Testmethoden (SIEGEL) herangezogen:

1. Friedman-Test für mehrfache Versuchspaare (Vergleich der durch Behandlung herbeigeführten Veränderungen der Durchlauf- bzw. verschwendeten Zeit gegenüber den entsprechenden Kontrollwerten zweier Tage vor- und nachher),

2. Kruskal-Wallis-Test (s. Ergebnisse der Reserpin-Behandlung),

3. Erweiterter Mediantest für geringen Versuchsumfang (Prüfung der Häufigkeit des Ausgleitens zwischen aufeinanderfolgenden Dosen).

Die Auswertung von Erhöhungen der Zahl der Fehler und Halte erfolgte nur informatorisch; die beobachteten Abweichungen waren relativ geringfügig.

Ergebnisse

a) Urethan und Phenyläthylbarbiturat. Die Versuche wurden nach intraperitonealer Gabe der Substanzen vornehmlich bei einem Abstand von 20 min zwischen Injektion und Start jedes Tieres durchgeführt, da auf Grund der Applikationsform ein rascher Eintritt der Effekte zu erwarten war. Einige Testungen nach einem Abstand von 3 Std dienten als Vergleich für die Versuche mit den anderen Substanzen.

Tabelle 1. *Übersicht zur Beeinflussung der Leistungskriterien durch Urethan und Phenyläthylbarbiturat*

	Dosis mg/kg i.p.	Start nach	Fehler D	Halte D	Ausgleiten		Durchlaufzeit (sec)		Verschwendete Zeit (sec)		BD_{50} mg/kg
					D	S	D	S	D	S	
Urethan	100	20 min	0,1	0,4	1,1	—	19,7	P=5%	0,3	—	
	200	20 min	0,6	1,1	3,8	P=1%	29,3	P=0,1%	4,4	—	
	300	20 min	0,1	1,4	12,8	P=0,1%	40,5	P=0,1%	1,9	—	
	400	20 min	4,0	6,2	16,0	P=0,1%	149,2	P=0,1%	60,1	P=1%	425
	500	20 min	—	—	—		300,0	P=0,1%	—		
	300	3 Std	0,6	1,3	5,0	P=1%	34,1	P=0,1%	3,0	P=2,5%	
Phenyl-äthyl-barbitur-saures Na	20	20 min	0,1	1,7	3,3	—	23,8	P=1%	2,4	—	
	30	20 min	1,0	2,4	6,1	P=0,1%	28,1	P=1%	4,5	—	
	40	20 min	0,6	3,6	9,5	P=0,1%	43,8	P=1%	8,7	—	
	50	20 min	4,3	5,0	14,0	P=0,1%	64,3	P=0,1%	25,0	P=1%	63
	75	20 min	—	—	—		300,0	P=0,1%	—		
	50	3 Std	8,1	6,0	19,8	P=0,1%	121,4	P=0,1%	72,0	P=1%	

D = durchschnittliche Zahl, bzw. Zeit für jeweils 8 Tiere pro Dosis; S = statistische Sicherung (vgl. hierzu Text); BD_{50} = mittlere Blockierungsdosis.

Die Durchschnittswerte für Fehler und Halte lassen eine positive Korrelierung erkennen. Nach 500 mg/kg Urethan bzw. 75 mg/kg Phenyläthylbarbiturat war die Registrierung einzelner Leistungskriterien infolge der extremen Koordinationsstörung nicht mehr möglich.

Die Ergebnisse sind in Tabelle 1 zusammengefaßt. Es ist ersichtlich, daß bei zunehmender Dosierung von Urethan und Phenyläthylbarbiturat die Verlängerung der Durchlaufzeit mit einer Steigerung der Häufigkeit des Ausgleitens einherging. Andere Leistungskriterien wurden im Sinne einer Verschlechterung erst nach Gaben beeinflußt, die im Bereich der mittleren Dosen für die Blockierung des Durchlaufes lagen. Es muß dabei berücksichtigt werden, daß das außerordentlich gehäufte Ausgleiten der Tiere eine Erschwerung der Orientierung zur Folge haben mußte.

Die Abweichungen von den entsprechenden Normalwerten waren 20 min nach Applikation von 300 mg/kg Urethan stärker ausgeprägt als

nach 3 Std, nach Gaben von 50 mg/kg Phenyläthylbarbiturat erwies sich der Einfluß bei der Testung zum späteren Zeitpunkt als stärker. Wie auch informatorische Versuche mit anderen Zeitabständen (zwischen 20 min und 3 Std) zeigten, führt deren Variierung zwar zu gewissen geringeren quantitativen Verschiebungen; sie ergibt jedoch keine neuen Gesichtspunkte, da die für die betreffenden Verbindungen charakteristischen Veränderungen der Leistungskriterien in ihren Relationen bestehen bleiben.

Die mittleren Blockierungsdosen (Dosen, nach deren Applikation die Hälfte der Tiere innerhalb 5 min den Durchlauf nicht bewältigten) lagen für Urethan zwischen dem vierten und fünften Teil der Letaldosis (LD_{50} = 1858 mg/kg Ratte i.p., eigene Bestimmung), für Phenyläthylbarbiturat etwa bei einem Drittel derselben (LD_{50} = 190 mg/kg Ratte i.p., SPECTOR) für einen Testabstand von 20 min nach Injektion. Am Tage nach der Behandlung vorwiegend mit den hohen Dosen beider Substanzen ließ sich eine Verlängerung der Durchlaufzeit bei deutlicher Vermehrung der Halte beobachten. Normale Leistungskriterien waren gewöhnlich am 2. Tage nach der Applikation wieder erreicht.

Tabelle 2. *Veränderung der Leistungskriterien nach Chlorpromazin und Prothipendyl* (Erklärungen vgl. Tabelle 1)

	Dosis mg/kg i.p.	Start nach Std	Fehler D	Halte D	Ausgleiten D	Ausgleiten S	Durchlaufzeit (sec) D	Durchlaufzeit (sec) S	Verschwendete Zeit (sec) D	Verschwendete Zeit (sec) S	BD_{50} mg/kg
Chlorpromazin-HCl	2	1	0	0,8	0,6	—	21,9	—	1,0	—	
	4	1	0,4	1,3	2,0	—	74,8	P=1%	43,9	—	
	5	1	1,2	2,5	1,6	—	82,2	P=0,1%	34,0	—	
	7	1	0,8	3,2	3,4	—	131,5	P=0,1%	82,0	P=2,5%	9,0
	14	1	0,3	2,3	0	—	300,0	P=0,1%	281,8	P=0,1%	
	7	3	0,1	2,8	1,8	—	73,4	P=0,1%	5,7	P=2,5%	
	14	3	0	2,5	0	—	275,1	P=0,1%	229,5	P=0,1%	
Prothipendyl-HCl	5	1	0,5	2,3	0,8	—	36,5	P=1%	5,3	—	
	10	1	0,3	2,4	1,0	—	50,6	P=0,1%	5,0	—	
	15	1	2,6	3,1	2,6	—	229,5	P=0,1%	181,3	P=1%	14,4
	20	1	0,8	2,8	1,0	—	300,0	P=0,1%	278,2	P=0,1%	
	5	3	0,3	1,6	0,4	—	26,6	—	3,1	—	
	10	3	0	2,0	0,6	—	31,0	P=1%	5,0	—	
	15	3	0,1	1,3	0,6	—	33,5	P=0,1%	1,4	—	

b) Chlorpromazin und Prothipendyl (Dominal). Tabelle 2 gibt eine Übersicht über die Effekte der beiden Neuroleptica nach intraperitonealer Verabreichung. Die Versuche 1 Std nach Applikation ergaben

ab 4 mg/kg Chlorpromazin eine signifikante Verlängerung der Durchlaufzeiten, die in höheren Dosen zunahm. Andere Leistungskriterien wurden dabei zunächst nicht sicher beeinflußt; die erwähnte Veränderung war somit im wesentlichen durch Verlangsamung der Laufgeschwindigkeit bedingt.

Die in den höheren Dosen aufgetretene signifikante Steigerung der verschwendeten Zeit war durch gelegentliches längeres Verharren der Tiere im Lauf und Aufhebung der Durchlauffähigkeit einzelner Tiere, nach 14 mg/kg aller Tiere bedingt, die dann nahezu über die gesamte Zeit (5 min) an einer Stelle im Anfang der Durchlaufstrecke verharrten. Das durchschnittliche Ausgleiten erfuhr keine wesentliche Erhöhung.

Die Beeinflussungen in den Versuchen 3 Std nach der Injektion traten eher etwas abgeschwächt gegenüber den entsprechenden nach 1 Std zutage, qualitativ waren die Wirkungen weitgehend gleichartig.

Die Testungen eine Stunde nach Prothipendylapplikation lieferten sehr ähnliche Effekte im Vergleich mit Chlorpromazin. Auch bei dieser Verbindung erwiesen sich die Abweichungen in den Versuchen mit 3 Std Abstand zum Zeitpunkt der Injektion als schwächer ausgeprägt; der Unterschied war deutlicher als bei Chlorpromazin.

Es läßt sich somit sagen, daß die wesentlichen Abweichungen der Leistungskriterien nach Gaben von Chlorpromazin oder Prothipendyl in einer deutlichen Verlangsamung des Laufes der Tiere und dosisabhängig dann in einer Blockierung des zielgerechten Laufes bestanden. Die mittlere Blockierungsdosis betrug in den 1 Std-Versuchen für beide Substanzen etwa den 15. bzw. 8. Teil der betreffenden LD_{50} (137 mg/kg Ratte Chlorpromazin i.p., eigene Bestimmung; 115 mg/kg Ratte Prothipendyl i.p., v. SCHLICHTEGROLL). Die Versuche am Tage nach der Verabreichung hoher Dosen von Chlorpromazin und Prothipendyl ergaben, daß bei einigen Tieren die Aufhebung der Durchlauffähigkeit (innerhalb 5 min) fortbestand; die Aktivität dieser Tiere (zahlreiche Fehler und Halte) war jedoch im Vergleich zum Versuchstag deutlich. Normalisierung der Leistungskriterien war bei allen Tieren am 3. Tag zu verzeichnen.

c) Reserpin. Anstelle der statistischen Bearbeitung der Durchlauf- bzw. verschwendeten Zeit im Friedman-Test wurde auf Grund der geringfügigeren Effekte des Reserpins insbesondere am Tag der Applikation und am folgenden Tage und der sich daraus ergebenden Notwendigkeit einer schärferen Beurteilung der Kruskal-Wallis-Test herangezogen. Tabelle 3 zeigt, daß Reserpin[1] in den Versuchen mit ein- und dreistündigem Abstand vom Zeitpunkt der Verabreichung selbst nach

[1] Reserpin wurde als Emulsion in 3%iger Gummi-arabicum-Lösung gleichfalls i.p. appliziert.

sehr hohen Dosen zu keinerlei signifikanten Veränderungen der normalen Durchlaufleistung führte.

Am Tage darauf (ohne erneute Applikation) ließen sich jedoch deutliche dosisabhängige Verlängerungen der Durchlaufzeit beobachten, ohne daß die verschwendete Zeit signifikant erhöht war: Somit ergab sich eine Verlangsamung der Laufgeschwindigkeit. Die offenbar dosisabhängige Steigerung der Fehler und Halte führte erst nach den beiden höchsten Gaben (verabreicht am Vortage) zu signifikanter Erhöhung der verschwendeten Zeit. Ein gesteigertes Ausgleiten wurde nicht registriert.

Tabelle 3. *Wirkung des Reserpins am Tage der Applikation und am darauffolgenden Tag, an dem keine Medikation erfolgte*

	Dosis mg/kg i.p.	Start nach Std	Fehler D	Halte D	Ausgleiten D	Ausgleiten S	Durchlaufzeit (sec) D	Durchlaufzeit (sec) S	Verschwendete Zeit (sec) D	Verschwendete Zeit (sec) S
Reserpin (Tag der Applikation)	2,5	1	0,1	0,4	0,1	—	15,4	—	0,4	—
	5,0	1	0	1,4	0	—	18,9	—	1,4	—
	7,5	1	0,1	1,9	0,3	—	21,5	—	1,7	—
	5,0	3	0	1,5	0,3	—	19,9	—	1,1	—
	7,5	3	0	0,9	0,3	—	18,0	—	0,9	—
	15,0	3	0	1,8	0,1	—	24,7	—	3,7	—
	30,0	3	0,3	0,8	0	—	21,8	—	1,6	—
Reserpin (folgender Tag)	2,5	1	0	0,9	0	—	17,3	—	0,7	—
	5,0	1	0,1	1,9	0,2	—	23,0	P=1%	3,1	—
	7,5	1	0,1	1,9	0,3	—	30,1	P=5%	5,1	—
	5,0	3	0,3	1,4	0	—	24,9	P=2,5%	2,5	—
	7,5	3	0,4	2,4	0,4	—	36,8	P=0,1%	7,6	—
	15,0	3	0,4	3,0	0,1	—	38,3	P=0,1%	7,8	P=2,5%
	30,0	3	7,3	7,0	0	—	91,8	P=0,1%	53,4	P=2,5%

Die betreffenden Angaben über Dosis und Start sind nur zur Charakterisierung der Gruppen wiederholt. Über Blockierungseffekte s. Text. Positive Korrelierung der Fehler und Halte am zweiten Tage.

Diese Wirkungen blieben in ähnlicher Ausbildung noch über mehrere weitere Tage bestehen. Bei fast allen der mit 15 bzw. 30 mg/kg behandelten Tiere resultierte, meist erst mehrere Tage nach der Applikation, eine Aufhebung der Durchlauffähigkeit; die angewendeten Dosen lagen aber bereits im letalen Bereich. Die Blockierung war jedoch nicht stets vom Tod des Tieres gefolgt.

d) Bemerkungen zum Verhalten der Tiere. Das Verhalten der behandelten Tiere zeigte einige Eigentümlichkeiten, die zur weiteren Differenzierung der einzelnen Verbindungen geeignet sind.

Nach Gaben der Hypnotica blieb die Tendenz der zielgerechten Bewegung erhalten. Selbst nach 500 mg/kg Urethan versuchten die Tiere, sich mit den Vorderextremitäten bei Anlähmung der Hinterextremitäten zielwärts zu ziehen.

Tiere, die sich beim Ausgleiten teilweise nur noch mit den Vorderextremitäten am Steg zu halten vermochten, kamen beim Heraufklimmen öfter in die dem Ziel entgegengesetzte Richtung. Die dadurch bedingte Fehlorientierung wurde von den Ratten gewöhnlich behoben: Einzelne Tiere, die nach 50 mg/kg Phenyläthylbarbiturat den Durchlauf in der Testzeit nicht bewältigten, waren doch bis kurz vor das Ziel gelangt und vermochten dieses bald danach zu erreichen.

Diese Tendenz der auf das Ziel gerichteten Fortbewegung war nach den höheren Chlorpromazin- oder Prothipendylgaben nicht zu beobachten: Fast allgemein kamen dann die Tiere über die ersten Teilstücke nicht hinaus und verharrten unter gelegentlichem Umwenden gewöhnlich an einer Stelle. Das Ausgleiten nach dieser Behandlung, das signifikante Erhöhungen nicht erreichte, war zudem viel uncharakteristischer als nach den Hypnotica; es wurde trotz seiner mehr angedeuteten Ausprägung voll bewertet (zuungunsten der Differenzierung).

Die Wirkungen des Reserpins zeigten Ähnlichkeit mit den Effekten der anderen beiden Neuroleptica bei zeitlicher Verschiebung. Die Blokkierung ließ sich auch bei längerer Beobachtung (über die normale Testzeit hinaus) nicht aufheben; ein am 14. Tag nach Applikation von 15 mg/kg Reserpin getestetes Tier gelangte innerhalb 2 Std nicht über Anfangsteil des Irrgartens hinaus. Andere Reserpinwirkungen wie Ptosis, Exsudation, Diarrhoe traten bald nach der Behandlung mit den höheren Dosen auf.

Diskussion

Aus den mitgeteilten Ergebnissen geht hervor, daß mit der Irrgartenmethode eine Trennung neuroleptischer und hypnotischer Wirkungen möglich ist. Urethan und Phenyläthylbarbiturat führten bei zunächst erhaltener Durchlauffähigkeit zu einer Koordinationsstörung; die Verhinderung des Durchlaufes nach hohen Dosen war durch diese bedingt. Nach Verabreichung der Neuroleptica stand die Verlangsamung der Laufgeschwindigkeit und schließlich die Blockierung der Befähigung zu zielgerechtem Lauf im Vordergrund. Die Auffassung, daß sich die Irrgartenmethode zur Differenzierung neuroleptischer und narkotischer Wirkung nicht eigne (Ther et al.), mag sich aus Befunden einiger Autoren ergeben haben, deren methodisches Vorgehen von unserem abwich.

Wenn man die sehr konstante Durchlauffähigkeit der Ratte im Irrgarten auf bedingt-reflektorische Abläufe zurückführt, so ist die Parallelität zu Ergebnissen offensichtlich, die mit anderen auf bedingten Reflexen beruhenden Untersuchungsverfahren erzielt wurden. Chlorpromazin ist in dieser Hinsicht vielfältig geprüft worden (COURVOISIER et al., GUHA et al., HARING et al., u. a.). Vergleichende Untersuchungen der Hypnotica und Neuroleptica wurden unter anderem von KNOLL und KNOLL vorgenommen. Die Autoren konnten an einem bedingten Fluchtreflex der Ratte zeigen, daß dieser durch Chlorpromazin und Reserpin selektiv gehemmt wurde, während Hypnotica die bedingten Reaktionen kaum beeinflußten.

Über die Wirkungen des Reserpins in bedingt-reflektorischen Untersuchungsverfahren wird allerdings in der Literatur nicht übereinstimmend berichtet; es sei in diesem Zusammenhang auf eine Übersicht von WERNER verwiesen, aus der die mögliche Bedeutung der Art der bedingt-reflektorischen Reaktion hervorgeht. Auch nach neurophysiologischen Untersuchungen sind die Wirkungen des Reserpins nicht ohne weiteres mit denen des Chlorpromazins vergleichbar. Für die Beurteilung und den Vergleich dürfte ferner die Berücksichtigung des langsamen Wirkungseintritts bedeutungsvoll sein. In unseren Befunden bewirkte selbst die Applikation sehr hoher Dosen bei Testung 3 Std später keine signifikanten Abweichungen, während am Tage darauf der Einfluß auch wesentlich niedrigerer Dosen deutlich wurde und über Tage bestehen blieb.

Es erhebt sich schließlich noch die Frage, ob andere depressiv auf das Zentralnervensystem wirkende Pharmaka ähnliche Effekte nach der Irrgartenmethode herbeiführen, wie sie für die hier geprüften Neuroleptica beobachtet wurden. In unseren bisherigen Versuchen mit verschiedenen Verbindungen anderer Pharmakagruppen konnten den Neuroleptica analoge Wirkungen nicht aufgefunden werden.

Zusammenfassung

Es wurden Untersuchungen an Ratten zur Klärung der Frage vorgenommen, ob Pharmaka aus der Gruppe der Hypnotica und der Neuroleptica nach der Irrgartenmethode verschiedene Änderungen in den Leistungen hervorrufen. An Hand der signifikanten Beeinflussung verschiedener Leistungskriterien ergab sich, daß das verwendete Untersuchungsverfahren zur Differenzierung hypnotischer und neuroleptischer Wirkungen geeignet ist. Während Urethan und Phenyläthylbarbiturat eine dosisabhängige Störung der Koordination bewirkten, führten Chlorpromazin und Prothipendyl zu einer Verlangsamung der Laufgeschwindigkeit und schließlich zu einer Blockierung zielgerechter Reaktionen. Reserpin verminderte gleichfalls die Laufgeschwindigkeit,

allerdings erst am der Injektion folgenden Tage. Die Ergebnisse zeigten auffällige Parallelität zu Befunden, die mit üblichen, auf bedingt-reflektorischen Abläufen beruhenden Methoden nach der Behandlung mit den gleichen Substanzen erhoben wurden.

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Ataractics and Strain Differences in Audiogenic Seizures in Mice

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The phenomenon of audiogenic seizures, long regarded as a paradoxical behavioral response, has been classified by several investigators as an epileptic-like response to the conflict-producing situation of auditory stress (BEVAN 1955). It has been found useful to evaluate psychoactive agents against this acute behavioral response. Several investigators have reported that certain ataractics afford different degrees of protection against the "end point" (the convulsion) of the "escape reaction" (PLOTNIKOFF and GREEN, 1957; LEHMANN et al., 1958; FINK and SWINYARD, 1959). However, the use of different strains of mice, routes of administration, and times of testing, not to mention a variety of test chambers and auditory sources has frequently compounded the difficulty of evaluating and comparing data of various investigators.

This study demonstrates differences in degree of protection against audiogenic seizures afforded by three known ataractics in two different strains of mice.

Methods

The chamber and sound source were described in an earlier paper (PLOTNIKOFF and GREEN, 1957). The seizure chamber consists of three compartments, an inner one, constructed of galvanized tin ($9^1/_2'' \times 9^1/_4'' \times 13^3/_4''$) and middle and outer ones of plywood ($11'' \times 11'' \times 14''$ and $14^1/_2'' \times 15'' \times 15''$ respectively). The space between the four sides of the inner and outer plywood compartments was filled with loose asbestos insulation for soundproofing. Essentially, the procedure consists of placing groups of five mice in the test chamber and exposing them to auditory stimulation for one minute. The stimulus was produced by two door bells, one of eight and one of ten volts, mounted on the right side of the inner galvanized tin chamber. The criteria used to measure protection in this study was the presence or absence of convulsions (clonic and tonic). Each drug was tested at three or more dose levels employing ten mice per dose. The dose which reduced the

total response to fifty percent of the control value (PD_{50}) and its standard error were estimated by the technique of MILLER and TAINTER, 1944. More quantitative measurement of the pre-convulsive escape reaction (running) will be reported at a future date.

Both chlorpromazine and meprobamate were administered by the oral route one hour before exposure to auditory stimulation. Reserpine was given by the intraperitoneal route 24 hours before the mice were tested.

The animals used for this study were inbred male DBA-1 mice and inbred male Swiss mice. The DBA strain[1] has a high rate of susceptibility to clonic and tonic convulsions (averaging 80 percent) for approximately one week (between 21 to 28 days of age).

The inbred male Swiss mice[2] have an exceedingly high susceptibility rate (averaging 95 percent clonic and tonic convulsions) for three weeks (between 21 to 42 days of age).

Results

Examination of the protective dose 50 percent (PD_{50}) values in Table 1 shows that it is extremely difficult to compare results from different strains and even sub-strains of mice. For example, in the case of chlorpromazine, a relatively small dose (PD_{50}, 4.8 mg/kg) was sufficient to inhibit convulsions in the DBA strain; in the Swiss strain, the same drug at a wide dosage range (0.625 to 160 mg/kg) had no inhibitory effect on the occurrence of convulsions. Only marked potentiation of convulsions was observed with the use of chlorpromazine in the inbred Swiss strain.

On the other hand, only a small difference in the degree of protection was shown by the use of reserpine in the two strains (DBA strain had a PD_{50} of 5 mg/kg and the Swiss strain a PD_{50} of 9.0 mg/kg).

The second and most significant difference between the two strains was demonstrated with the use of meprobamate. This agent was extremely active in antagonizing convulsions of the DBA strain (with a PD_{50} value of 4.5 mg/kg) and relatively weak against the convulsions of the Swiss strain (with a PD_{50} value of 90 mg/kg).

Discussion

The diametrically opposed data obtained with the use of chlorpromazine emphasize the difficulty in comparing results from different laboratories. For example, FINK and SWINYARD, concluded that phenothiazines are relatively weak antagonists of audiogenic seizures in mice

[1] DBA-1 strain obtained from the Jackson Memorial Laboratory, Bar Harbor, Maine.

[2] Swiss strain obtained from FLORA O'GRADY, 2336 Gunther Avenue, New York, New York.

of the Fring strain. The problem of strain difference is complicated even further when one considers that chlorpromazine is an active antagonist of convulsions in *noninbred* O'Grady Swiss mice (PD_{50} 5.0 mg/kg — PLOTNIKOFF). However, the same strain inbred for characteristics of short convulsive latency (five to ten seconds) and extremely low mortality rate (less than five percent) is *not* protected by chlorpromazine. This genetic property of inbreeding may be compared to mutant strains of bacteria which have been found useful for biochemical mechanism studies. In this regard, it has been reported by ABOOD and GERARD that susceptible mice have lower phosphate levels in their brains than nonsusceptible animals. It is suggested that other sub-

Table. *Protective dose 50 percent values of three ataractics against convulsions in two strains of mice*

Drug[1]	Route	Strain	
		DBA-1	Swiss (O'GRADY)
		PD_{50} mg/kg) $\pm$ S.E.	
Chlorpromazine	Oral	4.8 ± 0.67	Nonprotective[2]
Reserpine	I. P.	5.0 ± 0.52	9.0 ± 1.27
Meprobamate	Oral	4.5 ± 1.62	90.0 ± 0.57

[1] Sources of supply were as follows: *Chlorpromazine:* Smith, Kline and French Laboratories, Inc., Philadelphia, Pa. *Reserpine:* Chas, Pfizer and Co., Inc., New York, N.Y. *Meprobamate:* Wallace Laboratories, Inc., New Brunswick, N. J.

[2] Tested at a dosage range of 0.625 to 160 mg/kg.

strains of strains known to be susceptible to audiogenic seizures be inbred for particular characteristics such as long latency of convulsion, moderate to high mortality rate, clonic convulsion, spastic-type convulsion, and tonic convulsion, etc. It is conceivable that other differences in protection by various psychoactive agents may be uncovered. Studies of this nature may provide a means of characterizing new compounds and studying mechanism problems.

There are several conflicting reports on the action of reserpine against audiogenic seizures (TRIPOD, 1954; PLOTNIKOFF and GREEN, 1957 and 1958; BEVAN and MCCHINN, 1957; BIELEC, 1959, FINK and SWINYARD, 1959). In most cases, the critical points of difference appear to be the times of tresting and the routes of administration of the drug. The latter variable could be important in view of GLAZKO's report that reserpine is hydrolyzed to methyl reserpine. PLOTNIKOFF (1958) reported significant differences in the degree of protection afforded by reserpine when the oral and intraperitoneal routes were compared. Furthermore, the actual peak time of activity of reserpine against audiogenic seizures may be closer to 24 hours when one considers the fact that pharmacological

effects such as sedation last for days. This variable of peak time is being investigated and will be reported in a separate study. Finally, the conflicting reports may simply be another example of strain difference.

The results of this study prove the value of using several strains of mice to characterize the potency of new compounds in relationship to known ones. Certainly a more careful evaluation would appear to be warranted. Of possibly greater importance is the unique opportunity made available by inbreeding to study the neurochemical mechanism of action of various psychoactive agents.

Summary

1. Chlorpromazine was active in antagonizing audiogenic seizures of the DBA-1 strain and nonprotective against seizures in an inbred Swiss strain (O'Grady).

2. Reserpine was found to be slightly more active against seizures in the DBA strain than in the Swiss strain.

3. Meprobamate was approximately 18 times more active against seizures in the DBA strain than in the Swiss strain.

4. It is suggested that strain differences be considered when neurotropic agents are evaluated against audiogenic seizures in mice.

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Effects of Morphine and Nalorphine upon Tooth Pulp Thresholds of Dogs in the Alert and Drowsy State*

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It is well known that morphine elevates the threshold for repetitive stimulation of the tooth pulp in dogs with chronically implanted electrodes (KOLL and REFFERT 1938; GOETZL et al. 1943; WIKLER 1950; BOREUS and SANDBERG 1955). However, opiates induce sleep which in itself may raise the "pain" threshold by 50 per cent (WOLFF et al., 1940). Therefore, it was important to determine if the elevation in tooth pulp threshold caused by morphine was secondary to the drowsiness it produced. This report offers some experimental evidence in the elucidation of this problem.

Chronic bipolar electrodes were implanted in the upper canine teeth of six mongrel dogs (7 to 10 kg) under pentobarbital anesthesia. By aseptic techniques Formex coated stainless steel wires were placed into two small cavities in the upper canines. The holes were sufficiently deep so that the pulp could be visualized through a thin layer of dentine. A small loop was made at the bared peripheral end of the wire and placed into the cavity which was then firmly packed with silver-mercury amalgam. Dental acrylic was placed over the cavity to insulate the tooth and to help prevent the wires from pulling out. The appropriately identified wires were led below the skin through the vestibule to the top of the scalp for ease of electrical stimulation. To prevent infection, each dog received 100,000 units of penicillin intramuscularly for 3 days after surgery. In order to maintain a constant environment all tooth pulp thresholds were taken in a relatively quiet room each morning, beginning 3 to 10 days postoperatively. To restrict extraneous movements the dog was placed in a stockade. Before the actual experiment the animal was throughly familiarized with the apparatus and environment. Each of the upper canines was stimulated separately to determine which tooth gave the most reproducible response. Subsequently, that tooth was used for the remainder of the study. Repetitive shocks were applied to the tooth via the bipolar electrodes. A Hunter interval timer triggered a Grass Model S4B stimulator and isolation unit. Square wave pulses of 1 millisecond duration usually at 100 cycles per second

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for 1 second were repeated every 3 to 5 minutes in order to determine the threshold intensity to produce the characteristic response. For purposes of comparison a frequency of 30 cycles per second was used in one dog. In some experiments both voltage and current were monitored. Inasmuch as the current thresholds paralleled the voltage thresholds the data were expressed in volts for reasons of convenience.

The responses produced by stimulation of the tooth pulp varied between dogs but were consistent in each individual animal. A sufficient period of training was needed for the observer to differentiate spontaneous movements from those caused by stimulation. The intensity of repetitive electrical stimulation of the tooth pulp required to elicit a characteristic reaction response varied with the state of the animal. If the dog was wide awake the threshold of stimulation was lower than when the animal was drowsy or lethargic. The criterion for a response was a definite motor movement such as opening the mouth, chewing, or licking. After a period of training when the thresholds were stabilized, control thresholds were obtained in both the alert and drowsy states on the day that morphine and nalorphine were administered. The alert state was considered that in which the eyes were open and the dog was aware of minor changes in the environment, vocalized, or made some motor movement indicating an aroused or awake condition. The drowsy state was defined as that in which the eyes were closed and the animal was quiet and unaware of minor stimuli in the environment. After relatively constant thresholds were obtained a dose of 2 mg/kg of morphine was given intravenously and antagonized with 1 mg/kg of nalorphine given intravenously. The effects of morphine on the tooth pulp thresholds were determined periodically every 5 to 10 minutes. At the time of maximal elevation of the tooth pulp threshold following morphine (usually within 30 to 60 minutes) nalorphine was administered. The peak effect of nalorphine was usually 6 to 15 minutes after injection. The data obtained at maximal effect are listed in table 1. The tooth pulp thresholds after morphine were obtained immediately after the animal was awakened from deep morphine narcosis by gentle tapping on the table. Thus, the animal under morphine was aroused and aware of his surroundings at the time that the tooth pulp was stimulated. Inspection of table 1 shows a consistent trend in the effects of various treatments in each dog. In each animal both the drowsy state alone and morphine produced an increase in the threshold voltage greater than that seen during the awake state. Nalorphine reduced the elevated threshold after morphine toward the control level. Individual differences in dogs are indicated since each animal responded at considerably different threshold voltages. In a 2 way classification analysis of variance this individual difference in dogs was significant at the 5 per cent probability level. A Student "t" paired comparison test was used on the different

combination of treatments summarized in table 1. The voltage required of elicit a response during the alert state was found to be significantly different ($P < .005$) from that in the drowsy state. When the threshold during the alert state was compared to that after morphine, a 2.5 per cent level of significance was obtained. The data also show that the elevation in tooth pulp theshold produced by morphine is greater than that of the drowsy state alone ($P < .05$). Threshold voltages after morphine were also significantly different from those after nalorphine antagonism.

Table 1. *Effects of morphine and nalorphine on the threshold voltages required to elicit a response to repetitive stimulation of the tooth pulp in chronic dogs*

Dog	Threshold in Volts ± S.D.[1]			
	Control State		Morphine (M) 2 mg/kg IV	Narlorphine (N) 1 mg/kg
	Alert (A)	Drowsy (D)		
I	3.0±0	4.0±0	7.0±0	5.0±0
VI	1.5±0	3.8± .3	5.3± .6	3.0±0
VII	2.0±0	6.0± .8	6.0±0	3.3± .4
VIII	3.8± .3	8.3± .6	14.7± .6	7.3± .6
X	10.3± .5	12.0±1	18.0±2	10.5±3.5
XII	9.5± .7	14.3± .4	26.0±0	9.7± .6

[1] The voltage for each observation was measured to the nearest 0.5 V, but the threshold listed is the mean of 2 to 4 observations. The standard deviations are given only as an index of the reproducibility of the observations but were not included in the student „t" paired comparison test. The pairs compared with their P values are as follows: A—D, <.005; A—M, <.025; D—M, <.05; M—N, <.05.

Similar results were obtained when an analysis of variance of the subdivisions of treatment was performed except that the analysis of variance differed from that of the Student "t" test in that the thresholds during the alert state were significantly different from that of the drowsy state only at the 7 per cent probability level. The discrepancy between these two tests is probably due to an overestimate of the true error in the analysis of variance since the residual term included both interaction and sampling error. The results indicate that the effect of morphine in elevating the threshold for repetitive stimulation of the tooth pulp in chronic dogs is greater than that due to drowsiness alone. After morphine, nalorphine is effective in lowering the tooth pulp threshold toward the control alert state.

Summary

The alteration of tooth pulp thresholds of dogs with chronically implanted electrodes was determined in the awake and drowsy states after morphine and nalorphine. The elevation in tooth pulp threshold was significantly greater after morphine than during the alert or drowsy state of the animal. Nalorphine antagonized this effect of morphine.

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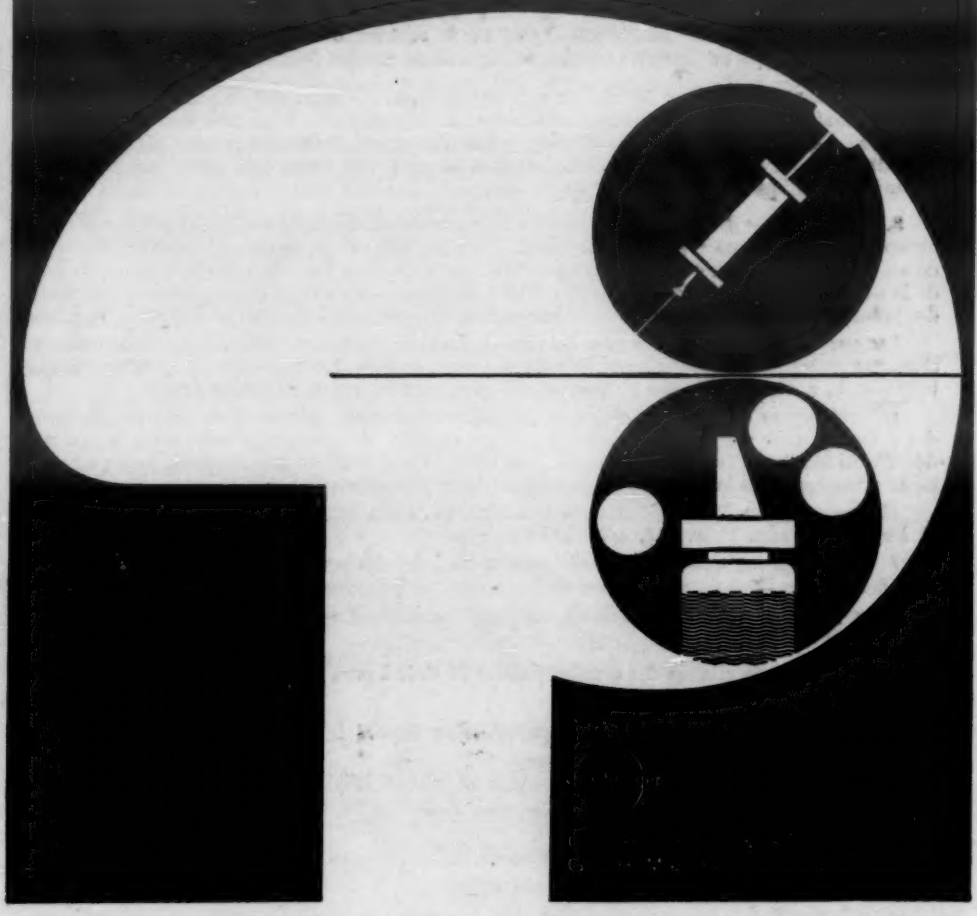

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